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Evaluation of a Mobile Health Intervention to Improve Anti-Retroviral Treatment Retention in South Africa

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Walden University
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Abstract

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by

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MPH, Boston University, 1998

BSc, University of California Los Angeles, 1996

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

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Abstract

South Africa has one of the highest HIV prevalence rates globally, with nearly 2.5 million people accessing antiretroviral treatment (ART) at the end of 2013. Retaining patients on ART has become a major problem in this country. When patients no longer show up for ART for unknown reasons, they are considered "lost to follow-up" (LTF). LTF is the highest contributor to ART attrition. This study, guided by the health belief model, evaluated the effectiveness of a technology-based, mobile health (mHealth) appointment reminder intervention on LTF among patients accessing ART services. The study ascertained differences in 6- and 12-month LTF rates between patients enrolled in the mHealth intervention (n = 832) and those in the standard of care comparison group (n = 918). A quantitative, retrospective cohort approach was used to answer the research questions using binary logistic regression analyses. The mHealth intervention was found to be significantly linked to lower likelihood of 6- and/or 12-month LTF among patients. There were 2 other key findings: a positive correlation between pregnancy and LTF, and a positive correlation between viral load increases and LTF. This study added evidence to the existing literature on the effectiveness of using mHealth-based interventions to improve HIV/AIDS care. Based on these findings, professionals should pay special attention to pregnant women and those clients with increasing viral loads to ensure they are not LTF. Positive social change that may result from this study is better health outcomes for patients on ART due to reduced risk of HIV related complications and other illnesses. This awareness would improve the lives of the patients, and positively impact their families, communities, and ultimately the global community, by reducing the overall impact of HIV disease.

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Dedication

I dedicate this dissertation to my dad - my silent strength. Your life messages still resonate in my mind. Thank you for your unconditional love, altruism, support and kindness, which not only allowed your children to become strong individuals but also impacted lives of thousands of people. Thank you for allowing me to pursue higher education and for your strong belief in prioritization of education for girls.

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Last but not least I want to acknowledge my family, friends and colleagues for supporting and cheering me on through this process.

Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction to the Study

Introduction

This study was a program evaluation of a mobile health (mHealth) - based patient appointment reminder intervention to improve retention in antiretroviral treatment (ART). The intervention was implemented in September 2012, at a large public sector ART clinic in an inner city setting in Johannesburg, South Africa.

Globally, Sub-Saharan Africa is the worst hit with the HIV/AIDS epidemic, with over 70% of HIV-positive people living in this part of the world (UNAIDS, 2012). This region has been very successful in enrolling individuals on ART (Micek et al., 2009). In South Africa there were over 2.5 million individuals on ART in the public sector as of October, 2013 (Ojikutu, 2008; PEPFAR annual report, 2013). Most people on ART obtain their care and treatment at public sector sites that are managed by the South African government.

As the ART programs have scaled up, the focus for most countries has moved from initiating patients on ART to retaining them, since being on ART is a lifelong commitment (Barnighausen et al., 2011). According to one study conducted in Sub-Saharan Africa, only 60% of patients were still on ART 2 years after starting treatment (Rosen, Fox, & Gill, 2007). A few studies have been published on interventions designed to improve patient retention, especially on tracing and following up with patients who drop out the ART program (Rosen & Ketlaphile, 2010). While these programs have demonstrated improvement in ART retention rates, there is a need for more interventions that account for the context of patients dropping out or the reasons why patients become lost to follow-up (LTF) (Miller, Ketlaphile, Rybaseck-Smith, & Rosen, 2010). LTF is defined as the disappearance of individuals from ART for no known reason. The US Government's definition for LTF is patients who have not returned to their ART clinics for

follow-up appointments or medicine pick up in more than 3 consecutive months (PEPFAR, 2007). It is the largest contributor to ART attrition, followed by death (Rosen & Ketlhapile, 2010).

One approach that may be useful withtackling the LTF issue is mHealth. mHealth is "the practice of medical and public health via mobile communication devices" (Catalani, Philbrick, Fraser, Mechael, & Israelski, 2013, p. 17), and it has numerous applications in the field of public health (Rodrigues et al., 2012; Tomlinson, Rotheram-Borus, Swartz, & Tsai, 2013). mHealth is a growing field. It is considered to have great potential for strengthening health service delivery which can lead to positive health outcomes, especially in resource-poor countries (Free et al., 2013), where the mobile phone is the fastest growing communication sector (Bahadur & Murray, 2010). The existing research and knowledge base around HIV/AIDS and mHealth primarily pertains to pilot projects, with a few qualitative studies and a handful of clinical trials (Bahadur & Murray, 2010). There is a gap in the literature on (a) outcomes of full-scale mHealth interventions to reduce missed ART follow-up appointments and (b) LTF rates among patients on ART. This study sought to obtain evidence on the outcomes of an intervention—implemented following formative and pilot research phases—in an effort to reduce the gap in the literature.

Improving retention in HIV care and treatment by reducing LTF are priority areas for the South African Department of Health (South African National Strategic Plan on HIV, STIs and TB 2012-2016, 2012). The positive social change implication of this intervention and its evaluation are significant as improved retention will lead to better patient health outcomes.

This chapter covers the following topics: a summary of the issue based on data from the scientific literature, problem statement, purpose of the study, methodology, research questions

and hypotheses, the theoretical framework, variables and their definitions, assumptions, scope, limitations, and significance of this study to the field of HIV/AIDS.

Background

Globally, there has been a surge in access to ART over the last few years, with a 20-fold increase in Sub-Saharan Africa (Micek et al., 2009). Access to ART has dramatically increased in the last few years in South Africa since the government rolled out its ART program in 2004. The country has the largest ART program in Sub-Saharan Africa with over 2.5 million people on ART in the public sector as of October, 2013 (Ojikutu, 2008; PEPFAR annual report, 2013).

Treatment Retention

While great strides have been made initiating patients on ART, low patient adherence and retention in HIV treatment have raised concerns about long-term outcomes (Maskew, MacPhail, Menezes, & Rubel, 2007). Rosen et al., (2007), conducted a systematic file review of ART programs in Sub-Saharan Africa and found that, overall, 25% of patients had dropped out by end of Year 1 of ART initiation, with this number rising to 40% by Year 2 on ART. Researchers in Malawi found that the median time between ART initiation and patients dropping out was 4.3 months (Yu et al., 2007). Dalal., et al (2007), found the median time between initiation on ART and first missed appointment at a public sector, tertiary hospital serving the inner city of Johannesburg, South Africa, to be 84 days (IQR 43-168 days, range 13-392 days).

LTF and death are the most commonly identified reasons for attrition from ART (Rosen et al., 2007). Approximately 56% of the treatment attrition is a result of LTF and another 40% is due to death (de Pee, 2010). LTF is a major issue for the South African ART program too. LTF rates from a multi-site, patient file audit at public sector clinics in two provinces in South Africa between 2006 and 2009 were found to be between 14-25%, with the largest proportion of

patients becoming LTF within the first 6 months of starting ART (Jaffer et al., 2007). A large public sector clinic with over 7,000 patients enrolled on ART in Johannesburg had a LTF rate of 16.4% among patients initiating ART over a 4-year period. Forty percent of the individuals at this clinic became LTF in the first 3 months after starting on ART (Rosen & Ketlhapile, 2010).

LTF is a major public health issue because patients who discontinue ART are at high risk of developing virological failure, acquiring opportunistic infections, and early mortality (Rosen et al., 2007; Unge et al., 2010). Harries, Zachariah, Lawn and Rosen (2010), conducted a meta-analysis of 16 studies in Sub-Saharan Africa and found that 20-60% of patients who were identified as LTF had died. Researchers in Malawi found that about 50% of the patients who had been identified as LTF had died, most dying soon after they missed their clinic follow-up appointment (Yu et al., 2007). Dalal et al., (2007), conducted a study at an ART clinic in a tertiary government hospital in Johannesburg, South Africa and found that one in six patients initiating ART were LTF. Once again, approximately 50% had died; a majority died within 30 days of missing their appointments (Dalal et al., 2007).

Missed appointments and LTF

Missed clinical appointments have been found to be a significant risk factor for developing virological failure and AIDS-defining illnesses (Lucas, Chaisson & Moore, 1999; Rastegar, Fingerhood & Jasinki, 2003), and death (Park et al., 2007). Viral resistance can develop quickly in an individual with poor adherence to ART. It can occur after only 11-30% missed ARV doses (Maskew et al., 2007). Missed appointments can also negatively impact health service quality because they can increase cost and lower efficiency of service delivery (Guy et al., 2012). Results from a South African study to ascertain the relationship between missed appointments early in the treatment phase of patients initiating ART and the health

outcomes of the patients indicated that in a 12-month period after initiating ART, only 65% of individuals attended all follow-up visits as scheduled. Of these, 2.6% of the patients had died and 6.2% were LTF. In addition, a higher number of missed clinical appointments were found to be associated with increased risk of mortality and LTF during the study period. The researchers also found that patients who missed three or more ART or clinical appointments were at high risk of low CD4 improvement. Furthermore, patients with three or more missed ART appointments were at increased risk of not achieving viral suppression by 6 months compared to the patients who did not miss any appointments (Brennan, Maskew, Sanne, & Fox 2010).

Regular clinic visits reflect good retention in care among patients on ART (Geng et al., 2010). Poor retention in care is reflective of low treatment adherence and of treatment cessation. Once treatment is interrupted, the effects of ART can quickly reverse and cause harm to the patients (Geng et al., 2010). Patient tracking has been recommended by some researchers while others have suggested some form of reminder system, which could reduce the rate of missed appointments (Dalal et al., 2007; Kliner, Knight, Mamvura & Wright, 2013). Other researchers have recommended implementing a patient tracer program, whereby patients missing their clinic appointments are contacted and asked to return to the clinic in a timely manner (Yu et al., 2007). Researchers studying the effectiveness of tracer projects have found improvements in patients returning to the facility after being contacted by a patient tracer. In a Kenya-based study, the rate of return of patients was found to be 65% and 49% in urban and rural areas respectively (Rosen & Ketlhapile, 2010). However, this type of intervention can be resource intensive, based on patient load per tracer, follow-up workers' salaries, transportation, and communication costs (Rosen & Ketlhapile, 2010). Therefore, there is ongoing search for alternate, efficient, and cost-

effective ways of tracing or communicating with patients to help them maintain good appointment adherence and retention in care.

Some of the reasons documented for missed appointments include forgetfulness, confusion regarding follow-up appointment dates, relocation, illness, hospitalization, transportation cost, side effects, death, and insufficient medication supply (Dalal et al., 2007; Maskew et al., 2007). Forgetting appointments is a common reason given by patients in a variety of health care settings (Guy et al., 2012; Kliner et al., 2013; Leong et al., 2006). The intervention evaluated by this study aimed to reduce appointment forgetfulness among patients on ART by sending them multiple reminders.

Mobile Health technology to improve health services

mHealth is defined as "the practice of medical and public health via mobile communication devices" (Catalani et al., 2013, p.13). Mobile technology includes cell phones, patient monitoring devices, personal digital assistants, and other equipment. (Bahadur & Murray, 2010). mHealth is a rapidly growing field. It is considered to have a great potential for strengthening health service delivery and leading to positive health outcomes especially in resource poor countries (Free et al., 2013). The acceptance of cell phones and their low cost has led to the quick uptake of mHealth technology in health services (Rodrigues et al., 2012).

mHealth has great potential for success in South Africa since the country has one of the highest proportions of mobile phones per capita, with over 90% of people having a mobile phone subscription (Leon, Schneider & Daviaud, 2012). Researchers exploring the feasibility and acceptability of mHealth related interventions in the South African population found a high level of interest and acceptability (Crankshaw et al., 2010). The South African government has also shown a keen interest in the use of mHealth technology in the public health care sector. In 2012,

the National Department of Health (NDoH) circulated a comprehensive eHealth strategy, which included the need for development, implementation, and evaluation of mHealth interventions to strengthen the public health sector (NDoH, 2012). In addition, there is growing support by the United States government, the World Health Organization, multinational companies, and other private entities (such as the cell phone network providers) to develop, implement, and evaluate innovative mHealth interventions to help strengthen the South African government's response to the HIV epidemic.

SMS-related interventions in HIV care and treatment

SMS or text messaging is a well-established technology that is used around the world. It is a cheap and efficient method of two-way communication, which costs much less than a cell phone call. Over the last few years, SMS has become the most prevalent mHealth technology application (Bahadur & Murray, 2010; Leong et al., 2006). Bahadur and Murray (2010), conducted a literature review between February and December 2008, to examine the use of SMS in health care settings. They found SMS to be an efficient, cost-effective, and appropriate technology for strengthening various health services sectors. However, Bahadur and Murray noted that some researchers were skeptical about the evidence for the effectiveness of SMS, since many of the reports or articles generated were from pilot projects or feasibility studies. They concluded that while SMS has been found to be effective in the public health sector, there is a need for further rigorous review of the benefits of this technology to improve health services in South Africa (Bahadur & Murray, 2010). In addition, none of the studies reported by Bahadur and Murray pertained to use of SMS to improve ART clinic attendance.

SMS to improve adherence on ART

Patient adherence to ART is crucial for continued benefits of ART in avoiding the development of viral resistance, reducing opportunistic infections, and early mortality (Rosen et al., 2007). In addition, adherence to ART has been linked to improved health outcomes; adherence is important to contain undue program costs (Lester et al., 2010). Since adherence is crucial for ART success, a number of interventions have been developed and implemented over the last few years. These have ranged from direct administration of ART, provision of financial incentives, education, additional counseling regarding adherence, facilitation of social support, and electronic and phone reminders (Rodrigues et al., 2012). In the last 3–5 years, a handful of studies have been conducted in resource-constrained countries that explored the use of SMS in improving ART adherence. These studies, which have included RCTs, have found an overall positive correlation between SMS or other mHealth intervention and increase in adherence to ART (Lester et al., 2010; Pop-Eleches et al., 2011; Rodrigues et al., 2012).

SMS for Clinic Appointment Reminders

Use of SMS to improve clinic appointment adherence in primary health care and other settings has been recorded by some studies; however, studies looking at SMS for improving ART appointment reminders have been minimal in the peer-reviewed or published literature. SMS reminders have been found to be effective in improving follow-up appointment adherence in numerous health care settings, including primary health care (Leong et al., 2006), medical male circumcision (Odeny et al., 2012), pediatrics, ophthalmology, orthodontics, and preventive health (Guy et al., 2012).

The importance of adherence to and retention in care of patients on ART is well documented in the scientific literature, along with the need for interventions to tackle these

issues. mHealth is a rapidly growing field and researchers have found strong evidence of associations between mHealth and HIV treatment adherence in a handful of clinical trials. However, there is a need for more information from program outcomes and clinical trials (Bahadur & Murray, 2010). In addition, there is a gap in the peer- reviewed and grey literature on studies that examine the effectiveness of SMS on improving ART clinic appointment adherence among patients receiving ART services in South Africa.

This study was a program evaluation of an appointment reminder intervention, which was rolled out at a large government funded ART clinic in Johannesburg, South Africa, with over 16,000 patients enrolled on ART since 2004. This study was important because it attempted to fill the gap in the literature about the use and effectiveness of mHealth to strengthen the public sector HIV/AIDS treatment programs in South Africa. The appointment reminder intervention was developed after a comprehensive project development cycle, which included formative studies (feasibility and acceptability studies), and a pilot phase.

Problem Statement

ART has been successfully scaled up globally and specifically in resource-limited settings such as Sub-Saharan Africa, leading to improvements in health outcomes of HIV-positive individuals (Brennan et al., 2010). However as programs have scaled up, treatment attrition has become an issue. LTF is the largest contributor to attrition, followed by death (Rosen & Ketlhapile, 2010). People who are HIV positive are expected to take the antiretrovirals (ARVs) for the rest of their lives to suppress viral replication (Ketlhapile, Rybasack-Smith & Rosen, 2010). Thus, adherence to ART is also expected to be life-long (De Pee, Grede, Forsythe & Bloem, 2012). As mentioned earlier, nonadherence to the ART regimen can lead to development of viral resistance, opportunistic infections, treatment failure, and early mortality

(Unge et al., 2010). Despite the known risks associated with nonadherence to ART, LTF and low treatment adherence remain a major challenge (Brennan et al., 2010).

Following the emergence of evidence of high LTF rates in the HIV/AIDS programs; studies have been undertaken over the last 5–7 years to (a) identify the LTF rates globally (Dalal et al., 2007; Rosen et al., 2007; Yu et al., 2007), (b) understand the reasons for LTF (Miller et al, 2010), (c) ascertain the impact of LTF on patient health outcomes, and (d) determine outcomes of interventions such as patient tracer programs using clinic and/or community-based individuals to bring the patients back to the clinic (Rose & Ketlhapile, 2010). Studies have also been conducted on use of innovative methodologies and technologies to improve adherence to ART (Lester et al., 2010). Some of the conclusions and recommendations from these studies were as follows:

- Interventions are needed to respond to the reasons for LTF (Unge et al., 2010).
- More evidence is needed on the effectiveness of interventions designed to improve short- and long-term retention in ART (Barnighausen et al., 2011).
- The work must move beyond pilots to ascertain the outcomes of implemented interventions (Bahadur & Murray, 2010),
- More evidence is needed from studies conducted in resource-limited settings, since most evidence is from resource-rich settings (Barnighausen et al., 2011).
- Ascertain the results from innovation- and context-based interventions, which are developed based on the reasons for LTF (Unge et al., 2010).

Most of these conclusions reflect gaps in the current literature. The scope of this evaluation study was limited to ascertaining the role of mHealth to reduce missed appointments and lower resulting LTF. Nonetheless, both the appointment reminder intervention and its

evaluation were based on some of the above mentioned recommendations and conclusions found in the literature. The appointment reminder intervention was developed in response to the issue of appointment forgetfulness among patients on ART. It was rolled out following a formative and pilot research phase, and conducted in a resource limited setting. The intervention was designed to prevent the occurrence of LTF among patients on ART; it was also a way for the clinic to keep in touch with its clients.

Purpose of the Study

This quantitative, retrospective, cohort study analyzed existing secondary data. The study purpose was to evaluate the effectiveness of a mHealth appointment reminder intervention to improve retention in care of patients by reducing LTF rates among patients on ART. The intent was to compare LTF outcomes between the intervention and comparison groups at two points in time. The intervention group included individuals on ART who enrolled in the intervention between September 1, 2012 and February 28, 2013. The comparison group consisted of randomly selected individuals on ART at the clinic who were not enrolled in the intervention. Individuals in both the intervention and comparison groups were assigned to one of six cohorts based on their time on ART as at September 1, 2012. The six cohorts (listed below) were formed based on historical LTF information found from a patient file review conducted at this clinic in 2009.

Cohort 1: Individuals initiated on ART between September 1, 2012 and February 28, 2013.

Cohort 2: Individuals initiated on ART from 1-6 months prior to September 1, 2012.

Cohort 3: Individuals initiated on ART from 7-12 months prior to September 1, 2012.

Cohort 4: Individuals initiated on ART from 13-24 months prior to September 1, 2012.

Cohort 5: Individuals initiated on ART from 25-36 months prior to September1, 2012.

Cohort 6: Initiated on ART more than 36 months prior to September 1, 2012.

The independent variable was the presence or absence of the ART appointment reminder intervention. The dependent variables were LTF at 6 and 12 months from September 1, 2012. The two time periods were selected based on evidence from mHealth-based ART adherence studies found in the literature. These studies found significant differences in adherence to ART in the 6- and 12-month timeframes (Lester et al., 2010; Rodrigues et al., 2012). LTF for the comparison group was determined to be June 1, 2013, and December 1, 2013 respectively (90 days after 6 and 12 months from September 1, 2012 – the start date of the intervention, based on the PEPFAR definition of LTF). Age, gender, baseline CD4 count, concurrent illnesses, ART regimen, and ART side effects were considered covariate variables for this study.

Research Questions and Hypotheses

This study was guided by the following research questions and hypotheses:

Research Question 1. Is there a difference in 6-month LTF rates between clients in the ART appointment reminder intervention and clients in the standard of care comparison group who did not receive the intervention, at Ward 21 in HCHC in Johannesburg, South Africa, after controlling for the identified covariates?

$H_{o1.}$ There are no statistically significant decreases in the likelihood of 6-month LTF for clients on ART who received the appointment reminder intervention when compared to clients in the standard of care comparison group.

$H_{a1.}$ There are statistically significant decreases in the likelihood of 6-month LTF for clients on ART who received the appointment reminder intervention when compared to clients in the standard of care comparison group.

Research Question 2. Is there a difference in 12-month LTF rates between clients in the ART appointment reminder intervention and clients in the standard of care comparison group who did not receive the intervention, at Ward 21 in HCHC in Johannesburg, South Africa after controlling for the identified covariates?

$H_{o2.}$ There are no statistically significant decreases in the likelihood of 12-month LTF for clients on ART who received the appointment reminder intervention when compared to clients in the standard of care comparison group.

$H_{a2.}$ There are statistically significant decreases in the likelihood of 12-month LTF for clients on ART who received the appointment reminder intervention when compared to clients in the standard of care comparison group.

Basic demographic information, along with the ART initiation date, baseline CD4 count, ART side effects, and concurrent illnesses were collected at the beginning of the study.

Theoretical Framework for the Study

The theoretical foundation for this study was the health belief model (HBM), which was developed to explain the relationship between health practices, behaviors, and health service utilization. Later, the model was revised to study people's behavioral responses to health-related conditions (Rosentock, Stretcher, & Becker, 1994; Janz & Becker, 1984). HBM is one of the most widely used theories in the field of public health. It has been the basis of numerous population studies to explain health-related behavior among different types of populations (Rosenstock et al., 1994), as well as health promotion and disease prevention interventions (Burke, 2014).

Initially, four perceptions formed the main constructs of HBM: perceived seriousness, perceived susceptibility, perceived benefits, and perceived barriers. Later, three other constructs

were added: cues to action, motivating factors, and self-efficacy. The latter three constructs affect the initial four perception-related constructs (Hayden, 2009).

The construct of interest for this study was "cues to action." A theoretical framework was not incorporated in the intervention design. However, some assumptions were made based on the literature review, that is, individuals who had agreed to partake in the appointment reminder intervention had experienced the various HBM perceptions when they initiated on ART and received adherence counseling from the clinic staff, which included information on following the ART regimen, looking out for side effects, and the importance of treatment adherence. Another assumption was that an individual's decision to initiate ART indicated that its perceived benefit had been recognized. Similarly, the individuals may have also perceived a benefit to the intervention offered, and believed that they had the ability to adhere to their follow-up clinic appointments.

The rationale for choosing the "cues to action" was that the appointment reminder was an external trigger to help participants maintain or improve their clinic appointment adherence behavior. As explained later in the chapter, the participants received three reminder "cues" between appointments (usually 30 days); one message was sent 2 weeks before the appointment, another a day before, and one the day after the appointment. In terms of the theoretical model, the key question of this study was: how effective were the cues to action in leading to the desired behavior or intervention?

Cues to action can be internal or external events, an exchange of information or communication that can influence human behavior change. The cues can be developed to raise awareness or provide specific advice to the target audience. Cues can also result from experiences of or events occurring in the individuals' circle of influence, for example, a similar

illness in a family member (Hayden, 2009). According to the HBM, one or more cues are generally required to serve as a "trigger" for initiation of healthy behavior (Olsen, Smith, Oei, & Douglas, 2010).

According to Olsen et al. (2010), HBM has been heavily investigated to predict adherence in several disease models, including for prostate cancer screening, mammography, and general health promoting behaviors. However, very few studies have measured the cues to action. Olsen et al. also mentioned that it is difficult to assess the effect of the cues prospectively, that is, before the behavior change happens. Thus cues to action studies are often designed as retrospective cross-sectional studies in order to understand the effects of the prompts on the desired behavior modification (Olsen et al., 2010). This was a key point in this study's development phase, which was designed as a retrospective assessment of the appointment reminder cue to improve clinic appointment adherence among individuals on ART. Some of the HIV/AIDS-related studies based on HBM constructs and conducted in the international health arena used different cues to action methodologies, such as drama or song, to increase HIV/AIDS knowledge and to remind participants to adopt safer sexual behaviors (Bosompra, 2007).

Rochon et al., (2011) conducted a qualitative study to ascertain feasible communication strategies that could influence ART adherence. The authors found that cues to action was one of the acceptable and feasible constructs for communicating adherence messages to patients on ART (Rochon et al., 2011). The results from the study indicated the acceptability and feasibility of using cues to improve adherence on ART, thus strengthening the rationale for this study to test whether appointment reminders would be effective in bringing about adherence (attending all appointments) and thus lower LTF rates in the population.

Nature of the Study

The rationale for designing this study as a retrospective cohort study was that it was an outcome evaluation of an appointment reminder intervention, which was implemented in September 2012. The goal was to ascertain the effectiveness of the intervention in reducing LTF among patients on ART at the clinic. Retrospective project and clinic data was used in this study to answer the research questions. A quantitative method of inquiry was chosen for this evaluation as it would yield the information required to answer the research questions.

The key independent variable for this study was the presence or absence of the intervention. Individuals enrolled in the intervention group should have received three reminders for each appointment. Follow-up appointments were usually 1 month apart, although the clinic could have scheduled appointments every 2 months for some stable patients. The study covariates were age, gender, CD4 counts (first, baseline and current), ART regimen, concurrent illnesses, ART side effects, and viral load. There were two dependent variables in this study. These were LTF at 6 and 12 months after the intervention was implemented at the site. LTF outcome was determined when a patient had not returned to the ART clinic or picked up their ARVs for at least 3 consecutive months (PEPFAR SASI Manual, 2007). Individuals who died during the study period were noted but not included in the analysis.

Fieldworkers were hired by the mHealth team to recruit participants in the intervention and for data collection for the project. After a comprehensive training and mentoring phase, the fieldworkers were placed at Ward 21 and asked to be present at the clinic every day. They approached patients in the waiting room, ascertained if the patient was eligible to participate by asking if they were on ART, explained the intervention to qualifying patients, and asked them if they wanted to enroll. If the patients agreed to participate in the intervention, the fieldworkers

walked them through an informed consent process. The consent form was approved by the Wits University IRB, which is the regulatory body for the host institution that implemented the intervention. The mHealth team developed data capturing tools and an electronic database for the intervention. The field workers collected the information in the intake forms and transferred it to the database at the end of each day. The clinic uses an electronic patient management and a pharmacy dispensing system, which the project team accessed to obtain patients' demographic, clinical and follow-up appointment information. The team used patients' clinic ID numbers as identifiers in the intake forms and for the project database. They also assigned unique intervention IDs for the individuals enrolled in the intervention.

Permission was obtained from WRHI to request for the retrospective program data from September 2012 to June 2014. This would cover the twelve month plus 90 days follow-up period for all the individuals who enrolled in the intervention between September 2012 and February 2013. Determination of LTF at 90 days after the end of six months of enrollment was based on the PEPFAR definition of assigning the LTF status (PEPFAR SASI Manual, 2007). In addition, permission was obtained to request for retrospective data from the clinic database for demographic, clinical, and appointment information for the intervention and comparison groups.

The project data was in Microsoft Excel file format. Additional demographic and study related data were included in this database as relevant. All study data was cleaned (i.e., reviewed for errors) then exported to SPSS 21.0 for data analyses. All the study variables were assigned a variable name, with the variable values coded (e.g. male = 1 and female = 0). Descriptive statistics were computed for the study variables, inclusive of study covariates. The mean, standard deviation, and minimum and maximum values were computed for ratio variables and frequencies, and percentages were calculated for dichotomous and categorical variables.

Spearman's rho correlations and model chi-square analyses were conducted between each of the study covariates and the two dependent variables. Covariates found to be associated with the dependent variables with p-values of < 0.25 were included as predictor variables in the logistic regression analyses, performed to address the study research questions. The *p*-value criteria of < 0.25 for covariate association were used for analysis based on the assumption that a covariate may not be significantly associated independently but may contribute to the model in conjunction with other variables. Two binary logistic regression analyses were conducted for the two dependent variables, LTF at 6 months and 12 months. Binary logistic regression was selected for this study as the dependent variables were dichotomously coded and the relationship between the intervention and the outcomes of LTF could be determined when covariate variance was accounted for (Agresti, 2013). The model chi-square (χ^2) determined the significance of the overall regression model, while the classification table generated by the statistical tool determined correct classification of the dependent variable categories based on the predictors in the model (Agresti, 2013). The Hosmer-Lemeshow (H-L) statistic for logistic regression, which answers the question, "how best does my model fit the data?" was used as the model goodness-of-fit statistic (Allison 2013). In the regression model, any probability value of significance (p-value) less than or equal to 0.05 were considered statistically significant.

Definitions

The independent variable for this study was presence or absence of the appointment reminder intervention. Presence of intervention was defined as individuals at the clinic who enrolled in the appointment reminder intervention between September 1, 2012 and February 28, 2013. Absence of intervention was defined as all individuals who attended the clinic during the study period but did not enroll in the intervention. This group of individuals received the

standard of care provided by the clinic. Age and gender was collected as part of basic demographic information. Below are definition of key study variables and covariates:

Age. Client age at initiation of ART was used as a measure of age. Age is a ratio variable and was calculated in years.

Gender. Gender was a dichotomous variable where 1 = male and 0 = female.

ART Initiation Date. ART initiation date was the date the person started on ART at the clinic and considered as time zero for ART follow up.

Baseline CD4 count. Baseline CD4 was defined as the most recent CD4 count available within 3-6 months prior to ART initiation. CD4 count is the number of CD4 cells, a type of white cell that fights infection, in the body. A low baseline CD4 count can put a person at a high risk of getting sick. It can have an effect on adherence to ART appointment and loss to follow up. For the purpose of this study, Baseline CD4 was the most recent CD4 count available within 3-6 months prior to ART initiation (The ART Cohort Collaboration, 2011)

ART regimen. This covariate was a categorical variable based on two types of ART regimens commonly prescribed in the public sector sites in South Africa. Some patients in South Africa receive a combination prescription if ARV side effects and other physiological or psychological issues arise. The commonly prescribed regimens as per the National ART Treatment Guidelines, 2004 are:

First line: Regimen1a - d4T / 3TC / efavirenz; Regimen1b - d4T / 3TC / NVP

Second line: Regimen 2 - AZT / ddI / lopinavir / ritonavir

Concurrent illnesses. This covariate was based on the presence of concurrent illnesses as noted in the patient's records. These were any other illnesses or diseases that manifested in the patient and could have affected the patient's clinic attendance and LTF outcome. For example,

tuberculosis, mental health issues, cancer, herpes zoster and other illnesses. The concurrent illnesses was coded by the type of illness and number of occurrences.

ART side effects. This covariate was based on evidence of ART side effects as noted in the patient's records. These can cause unplanned delays in patient returning to the clinic for their appointments, therefore it is important to note these. These were coded by type of side effect and number of occurrences.

Loss to Follow up. Programmatically, Lost to Follow up is defined as the disappearance of the individuals from ART for no known reason (Rosen et al., 2007). For the purpose of this study a patient was considered lost to follow up if they had not been to the clinic or had not picked up their ARVs for at least 3 consecutive months. (PEPFAR Strategic Information Manual South Africa, 2007).

Virological failure. Plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support. (WHO, 2013); Virologic failure happens when anti-HIV medications cannot reduce the amount of virus in the blood. While taking medications, viral load drop or it repeatedly rises again after having dropped (NIH, 2014).

Assumptions

This study was based on the following assumptions:

- The study population was representative of the population on ART in any urban-based public health facility in South Africa. The population accessing services at the clinic was considered to be heterogeneous which was reflective of the catchment population of the clinic.
- The participants felt comfortable about their confidentiality when enrolling in the intervention and felt that they had an option to opt out. The fieldworkers were

trained to review the patient confidentiality information with the participants, and the participants were informed that they could opt out at any time. A separate SMS number was specially created which participants could use if they wanted to opt out of the intervention.

- Individuals who had agreed to partake in the appointment reminder intervention may have experienced the various HBM perceptions when they initiated on ART, and they had received adherence counseling from the clinic staff which included information on following the ART regimen, looking out for side effects, and the importance of treatment adherence. An individual's decision to initiate on ART may indicate that the individuals saw the perceived benefit of ART. The individual may have also seen a perceived benefit of the intervention offered and believed that they had the ability to be adherent to their follow-up clinic appointments.

The assumption regarding heterogeneity of the population was necessary to allow for generalizability to other urban populations in South Africa. The clinic population includes individuals from various social, economic and cultural backgrounds. Thus any strong tendencies or circumstances pertaining to social, economic, environmental, mental and other factors among individual participants that could grossly affect or skew the outcomes were not expected. The assumption regarding freedom to opt out was necessary since individuals self-selected to receive the appointment reminder intervention. The individuals should not have felt at any time that they were coerced into enrolling in the intervention. The assumption about the perceived benefit of being on ART was important as individuals needed to be at a particular level of readiness to consider and take advantage of the intervention as a useful tool to improve their health outcomes.

Scope and Delimitations

This study sought to ascertain the effectiveness of an appointment reminder intervention in reducing LTF rates among patients on ART in a resource-constrained setting. The intervention was developed based on the information found in the literature, which indicated a correlation between missed appointments with LTF (Brennan et al., 2010; Geng et al., 2010). As mentioned earlier, South Africa has made great strides in enrolling a large number of people on ART since the national ART roll out started in 2004. However, patient attrition from ART negatively affects the achievements, and the long-term effects of LTF have a worse impact on the individual's health as it puts them at undue risk of adverse events such as viral resistance and treatment failure (Rosen et al., 2007).

The intervention population included all adults on ART including pregnant women at the ART clinic, Ward 21, located at the HCHC in the inner city of Johannesburg, South Africa. Ward 21 had over 16,000 individuals on ART when the appointment reminder intervention was implemented. The study sample comprised all individuals who chose to enroll in the intervention (intervention group) during the defined study period, and a randomly selected sample of individuals on ART at the clinic but not enrolled in the intervention (comparison group). Children under 18 years old were excluded from the intervention and the study because there are different treatment guidelines and regimens for the pediatric population. The cues to action construct of the HBM was deemed to be the most relevant for the study's theoretical framework.

The study outcomes were generalizable to other urban settings in South Africa since the appointment reminder intervention was rolled out as a health services improvement intervention, and the fact that there was a treatment and a comparison group, along with the assumption that the individuals assessing the services at the clinic were representative of typical urban based

populations accessing public sector ART sites in South Africa. Some of the dynamics may be different in a rural setting and may need a separate inquiry.

Limitations

This study was subject to the following limitations:

- The lack of random selection of individuals to enroll in the intervention. The intervention was rolled out as a health services improvement project and not as a research study. It had been piloted and found to be effective in improving adherence to clinic appointments at a primary health facility in the inner city of Johannesburg. When the intervention was implemented, patients on ART attending the clinic were approached and the intervention was offered to them. The intervention enrollment period was from September 2012 to December 2013. Based on the recruitment design, the participants self-selected to receive the intervention, and thus there was a risk of selection bias. All individuals enrolled in the intervention between September 2012 and February, 2013 (the study period), who received the intervention as planned without major information missing were assigned to the intervention group. A partly purposeful, partly random stratified approach was used to select individuals on ART at the clinic but not exposed to the intervention, for assignment to the control group.
- Following lessons learned from the pilot phase, the mHealth team made a major modification to the original project design. Instead of offering only the appointment reminder intervention to individuals newly (< 30 days) initiated on ART, all individuals on ART (regardless of time on ART) were offered the appointment reminder intervention along with weekly treatment adherence reminder messages for one year. While this modification was based on the lessons learned, it could have

affected the evaluation outcomes. It is impossible to confidently state if differences noted between the intervention and control groups were due to the appointment reminder or the adherence reminder intervention. An evaluation of the adherence reminder program may assist to distinguish the differences between the two interventions.

- Only a quantitative methodology was used. A mixed method would have been a more appropriate methodology as a qualitative component could have explained some of the participant behavior, decisions or nuances leading to the outcomes noted. These items were not easy to ascertain from a quantitative methodology alone. To this effect, the researcher has discussed with the mHealth team about them conducting a complimentary qualitative study using a sample of the study cohort to make the evaluation results more comprehensive. This study may be conducted at a later date.
- Since the study design required use of retrospective data, it was not possible to control the quality of the collected data. The mHealth team had incorporated some quality assurance mechanisms such as quality checks by the project coordinator, but it was not possible to ascertain how successful the team was at implementing these as planned or as stated in the recruitment Standard Operating Procedures.
- Given the sheer size of the HIV epidemic in South Africa, HIV is the focus of the government, donors and other international agencies agendas. For example, the minister of health started country wide HIV counseling and testing campaigns in 2010. These campaigns were in their second year in 2012 and were being scaled up by the NDoH as only 31% of HIV positive individuals were enrolled in ART (HSRC report, 2012). The South African public is constantly exposed to messages regarding

HIV prevention, testing and treatment from the government, donors, non-government organizations, community-based organizations and others. In addition, it is likely that given the high prevalence of HIV a large proportion of the population in South Africa has been affected by HIV directly or indirectly. Therefore, it is possible that the other experiences and exposures may have acted as cues to action for the study participants, and could have possibly driven the outcomes towards the null hypothesis.

- At the intervention design phase it was found that the South African public has a tendency to change their phone sim cards or their cell phone numbers frequently so the project would potentially not be able to send messages as planned. Two events that may have assisted in controlling this issue were that the government instituted a requirement for cell phone users to register their sim cards using their government issued identity card or passport numbers. This may have reduced the behavior of frequent changing of sim cards. Another intervention the team put in place in response to this issue was that they asked the clinic and pharmacy staff to ask the patients for updates to their contact information at each visit.

Significance

LTF is a major problem that affects the HIV/AIDS treatment programs globally, However, its impact are strongest in Sub-Saharan Africa and some developing countries because of the high HIV prevalence rate and poor access to and availability of health services. This evaluation and the related intervention have the potential to provide positive social change at a local, national policy and possibly global level. I expected the evaluation outcomes to provide evidence to fill some of the gaps in the literature around LTF, and use of mHealth as a viable tool in the field of HIV/AIDS.

As described in Chapter 2, there is a high acceptability of mHealth interventions by various stakeholders and the technology has the ability to reach a large number of populations in a short amount of time. In addition, mHealth-related interventions can offer individualized messages to the target population based on their needs. mHealth is an innovative way to promote health messages and improve health services in the developing and developed country contexts, simply because of the high cell phone penetration and its use globally.

Individuals who start on ART have to be followed regularly to make sure that they are adhering to the treatment regimen, and to identify any side effects or other issues arising at an early stage. mHealth is a tool that can assist with this need. The literature review conducted as part of this dissertation highlighted that while mHealth is a fast growing field, there are still gaps in the literature pertaining to the effectiveness of this technology in the field of HIV/AIDS. There is also an identified need for evidence-based information from mHealth based HIV/AIDS interventions, which have been fully implemented versus pilot projects (Bahadur & Murray, 2010). This is where the outcomes of this study could potentially contribute to the field. The appointment reminder intervention that this study evaluated was one of three interventions implemented and managed by the mHealth team at WRHI. The other two projects will be evaluated by the WRHI staff at a later date. Once the evaluations have been completed, the plan is to present the collective results to the South African NDoH and relevant funders. The information is meant to be used by the NDoH to inform policy and as relevant for possible roll out of the interventions at a national level. For the funders and other international agencies, the outcomes also provide viable options that could be replicated in other countries or serve as platforms for further funding and query.

Summary

In this chapter, a summary of the information found in the scientific and some grey literature around the issue of LTF and the current gaps was presented. This was followed by an overview of the methodology, the indirect and direct variables, the research questions and the relevant hypotheses, and the theoretical framework that the study was based on. An objective view of the study scope, limitations, and threats were provided. Cross cutting the various sections was the point about how the study could potentially impact positive social change and contribute to the field of HIV/AIDS using innovative solutions.

Chapter 1 provided a general overview of the study, including the topic of concern and the research methods. Chapter 2 includes findings from the literature review, gaps in the literature, the theoretical framework, and the need for this study.

Chapter 2: Literature Review

Introduction

The purpose of this study was to evaluate the effectiveness of a mHealth patient appointment reminder intervention to improve retention in care of ART patients by reducing LTF rates.

ART has been successfully scaled up globally—especially in resource-limited settings such as Sub-Saharan Africa—leading to improvements in health outcomes of HIV-positive individuals (Brennan et al., 2010). However as programs have scaled up, treatment attrition has become a major issue. LTF, defined as the disappearance of the individuals from ART for no known reason is the largest contributor to attrition, followed by death (Rosen & Ketlhapile, 2010). HIV positive individuals who are started on ART are expected to take the antiretrovirals (ARVs) for the rest of their lives to suppress viral replication (Ketlhapile et al., 2010). Non-adherence to the ART regimen can lead to development of: viral resistance, opportunistic infections, treatment failure and early mortality (Unge et al., 2010). Despite the known risks associated with non-adherence to ART, LTF and low treatment adherence remain a major challenge (Brennan et al., 2010). More evidence is needed on the effectiveness of interventions designed to improve short- and long-term retention in ART (Barnighausen et al., 2011).

This chapter includes: a summary of the information found during the literature review, the theoretical framework suggested for the study, a review of the problem under query, and evidence to support the need for this study to address the gap in the literature.

General information on the HIV epidemic both globally and in sub-Saharan Africa is provided at the beginning of this chapter followed by roll out and scale up of ART in Sub-Saharan Africa and specifically in South Africa. The issues of long-term sustainability of patients

on ART and LTF are discussed next followed by linkages between missed appointments and reduced adherence to ART, and retention in care. The role of mobile health (mHealth) technology in improving health services and particularly retention in care forms the second part of this chapter. The discussion starts with an overview of mHealth technology, followed by a review of mHealth studies to improve clinic appointment adherence. Use of SMS for appointment reminders to improve clinic attendance is the central component of this dissertation therefore it forms a large portion of the second half of this chapter. The chapter ends with a summary of the key information and gaps found in the literature; the need for the study, and provides a segue to Chapter 3.

The primary source of information for the literature review was peer-reviewed journals; however, some reports were also accessed, such as the WHO *Bulletin*, and United States and South African government documents. In addition, grey literature in the form of white papers, program reports, and conference presentations was accessed. The use of grey literature was kept to a minimum.

The literature search was carried out in two phases. Phase 1 involved searching PubMed, Medline, and EBSCO HOST databases using the following keywords: *HIV/AIDS in South Africa, Scale up of ART, HIV treatment retention in care, Loss to Follow up of patients on ART, interventions for Loss to follow up, mHealth technology, mHealth and HIV, mHealth and appointment reminders, and SMS for appointment reminders.* Phase 2 of the literature search involved review of the references found in the Phase 1 papers and conducting a search by specific titles. Phase 2 was found to be most effective in identifying specific articles on clinic appointment reminders. Note that the terms *SMS* and *text messaging* have been used interchangeably throughout this document.

mHealth is the overarching topic of interest however, the dissertation research question drills down to the use of SMS technology in improving patient retention on ART at public sector clinics in South Africa. Some general observations from the literature review are that since mHealth is a relatively new field, the articles found were mostly published in the last ten years. Numerous published studies pertained to the use and outcomes of mobile technology in the health arena, however, most of the studies were conducted in resource rich countries and in areas other than HIV care and treatment. Many of the mHealth articles were reviews and meta-analyses of previously published papers and grey literature versus new research. The new research found included a substantial amount of pilots and feasibility studies. That said, some of the new research were trials from Sub-Saharan Africa, and pertained to use of SMS in improving adherence to ART.

Theoretical Foundation

The theoretical foundation for this study was the Health Belief Model. This model was developed in the 1950s by three social psychologists: Godfrey Hochbaum, Irwin Rosenstock and Stephen Kegels, who were working for the United States Public Health service at the time. The model was originally developed to provide a systematic way to explain the reasons for failure of individuals to engage in preventive health measures. HBM was developed to explain the relationship between health practices, behaviors and health service utilization. Later, the model was revised to study people's behavioral responses to health-related conditions (Rosentock, Stretcher & Becker, 1988; Janz & Becker, 1984).

HBM is one of the most widely used theories in the field of public health. It has been the basis of numerous population studies to explain health related behavior among different types of populations (Rosenstock et al., 1994), and health promotion and disease prevention interventions

(Burke, 2014). HBM is referred to as an "interpersonal" theory. That is, it uses the individual's personal/internal knowledge and beliefs regarding the issue under study. It ascertains health behavior of individuals by examining the perceptions and attitudes individuals have towards illness and negative outcomes of certain actions (Burke, 2014). According to Hayden 2009, the essence of HBM is that health behavior is influenced by personal beliefs. This is reflected in the constructs that form the foundation of this model.

Initially, four perceptions formed the main constructs of HBM. These were: perceived seriousness, perceived susceptibility, perceived benefits, and perceived barriers. Later, three other constructs were added which were: cues to action, motivating factors, and self-efficacy. The latter three constructs affect the initial four perception related constructs (Hayden, 2009). The constructs lead to what has been coined as "Likelihood of Action" or behavior change (Janz & Becker, 1984).

Perceived Seriousness relates to a person's perception about the intensity or severity of a disease. While this perception often stems from information from medical resources, it may also result from an individual's perception of how the disease would negatively affect their wellbeing and their life in general (Hayden, 2009).

Perceived Susceptibility is based on an individual's perceived risk or susceptibility to acquire the disease. The behavior change can be directly proportional to the intensity of the perceived risk. That is, the stronger the perceived risk, the higher the probability of risk reducing behavior. On the flip side, the opposite can also be true. That is, when people believe that they are not at risk or have low susceptibility, then they may have more or continue with unhealthy behaviors. Public health practitioners have found that behavior change often occurs when there is a combined high perception of threat and severity of disease (Hayden, 2009).

Perceived Benefits is when a person sees the value or usefulness of the new behavior in reducing the risk of developing the disease outcome. This has been found to be particularly important for uptake of health screening related interventions such as colorectal cancer screening and others (Hayden, 2009).

Perceived barriers is related to the individual's perception of the barriers in bringing about the particular behavior change. The barriers could be personal, environmental, psychological, social, economic, cultural and others (Hayden, 2009).

Cues to action are internal or external events, information exchange, communication and other items, which can influence behavior change among individuals. The cues may be developed to raise awareness or provide advice or include personal symptoms or similar illness in a family member or a friend. The cues can be anything that can trigger a person to change behavior. The items or events listed above can act as cues for individuals to undertake a behavior change (Hayden, 2009). According to the HBM, one or more cues are generally required to serve as a "trigger" for initiation of healthy behavior (Olsen et al., 2010).

Motivating factors also known as modifying variables relate to the fact that the four original constructs of individual's perceptions and thus behavior change can be modified by external or internal variables such as education, personal experience with the disease, culture, motivation and others (Hayden, 2009).

Self-efficacy is the "belief in one's own ability to do something" (Hayden, 2009). It is based on the fact that individuals generally do something new if they believe that they can or have the capability to do it. For example, based on a perceived benefit, a person may believe that a new behavior may be beneficial, however, if the person does not believe that they are able to carry out the behavior change, then the chances of behavior change would be low.

As mentioned earlier, HBM has been applied in numerous public health settings and populations to study the correlation between the HBM constructs and desired behavior change. According to Conner and Norman, (1996) and Janz and Becker, (1984), the applications can be divided into three broad areas: 1) Preventive health behaviors including health promotion and health risk behaviors to avoid illness or injury. 2) Sick role behaviors, which refers to actions taken after a medical diagnosis of disease has been made and complying with a recommended medical regimen to restore health (Janz & Becker, 1984). 3) Clinic visit which includes clinical or health service utilization for any health reason. Janz and Becker (1984) conducted a review of 46 HBM related studies which they divided into one of the above listed three areas. Studies under the preventive health behaviors area included influenza and swine flu surveys, seatbelt use, exercise, nutrition, dental and medical checkups, drinking and driving, and others. Screening behavior related studies on Tay-Sachs disease screenings, practice of breast self-examination, and others. Sick behavior role studies included regimen compliance studies such as for hypertension, insulin and non-insulin dependent diabetic regimens, end stage renal disease, and others. Clinic visit studies were focused on use of clinical services for illness or disease symptoms, pediatric visits, preventive, acute and emergency clinical visits, and others. Overall, Janz and Becker found substantial evidence in the studies, which supported HBM constructs as key contributors to the prediction or explanation of the participants' behaviors being investigated in each of the studies (Janz & Becker, 1984).

The construct of interest for this study was "cues to action". A theoretical framework was not incorporated in the intervention design however, during the study design phase some assumptions were made based on the information found via the literature review. These were: the individuals who had agreed to partake in the appointment reminder intervention had experienced

the various HBM perceptions when they initiated on ART and received adherence counseling from the clinic staff which included information on following the ART regimen, looking out for side effects, and the importance of treatment adherence. An individual's decision to initiate on ART indicated that the individual saw the perceived benefit of ART. The individual may have also seen a perceived benefit of the intervention offered and believed that they had the ability to be adherent to their follow-up clinic appointments.

The rationale for choosing the "cues to action" was that the appointment reminder was an external trigger to assist the individuals to achieve the clinic appointment adherence behavior. As explained later in the chapter, the participants received three reminder "cues" in the time between appointments (usually 30 days); one message was sent a week before the appointment, another a day before and one the day after the appointment. The key question for the study in terms of the theoretical model was: how effective were the cues to action in leading to the desired behavior or intervention outcome? Figure 1 shows the basic elements of the proposed appointment reminder intervention HBM and the cue to action construct possibly leading to the desired behavior of clinic appointment adherence.

The cues to action construct of the HBM has been studied in various areas either as a component of the overall HBM constructs or as an independent entity. One study found in the literature was on the effect of the HBM constructs on weight loss related behavior among middle school girls. The researchers found cues to action to be the most important variable for predicting behavior intentions of weight loss among the study population (Park, 2011). Another study assessed predictors of intent to receive the H1N1 influenza vaccine among a convenience sample of college students and grocery store patrons. The investigators found that participants were

more likely to receive the vaccine if a physician provided the cue or recommended the vaccine (Coe, Gatewood, Moczygemba, Goode, & Beckner, 2012).

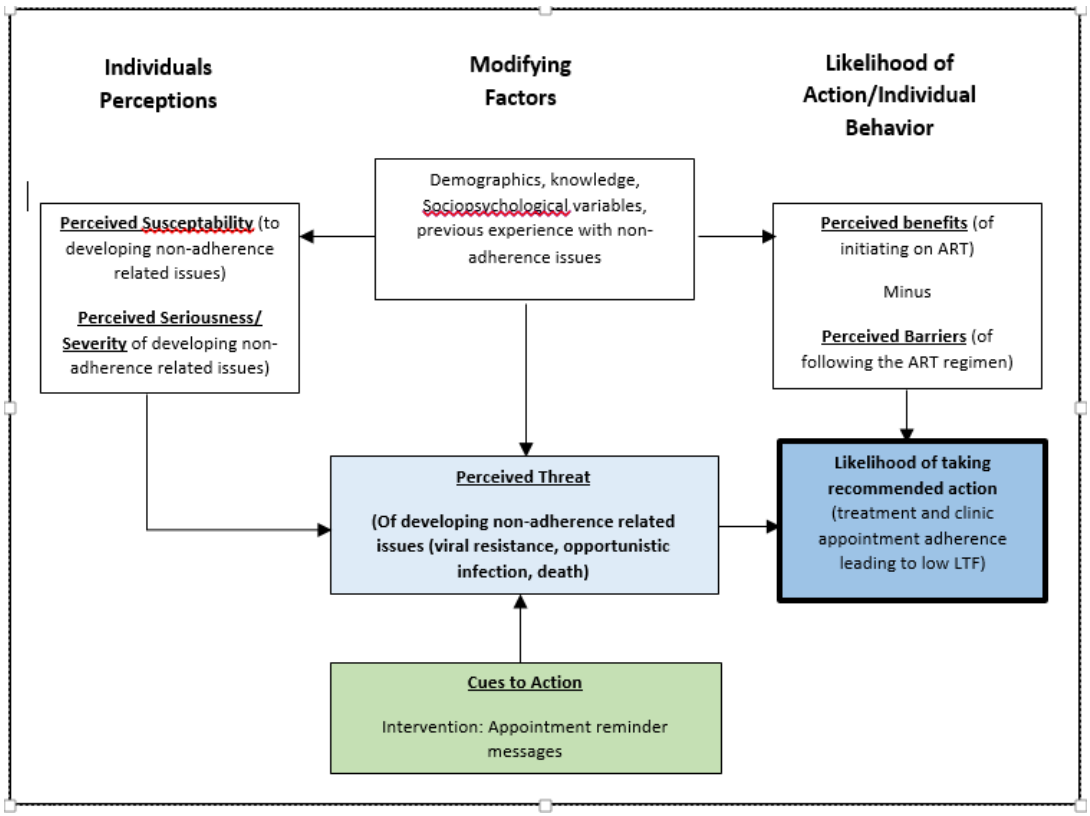

Figure 1. Elements of the HBM for the mHealth appointment reminder intervention. (Adapted from Burke E, n.d)

Another study focused on the cues to action construct for starting CPAP in obstructive sleep apnea and adherence over time (Olsen et al., 2010). According to Olsen et al., HBM has been heavily investigated to predict adherence in several disease models including for prostate cancer screening, mammography, and general health promoting behaviors, however, very few studies have measured the cues to action. Olsen et al. also mentioned that it is difficult to assess the effect of the cues prospectively, that is before the behavior change happens. Thus cues to action studies are often designed as retrospective cross sectional studies to understand the effects

of the prompts on the desired behavior modification (Olsen et al., 2010). This was a key point during the study development phase, and it was designed as a retrospective assessment of the appointment reminder cue to improve clinic appointment adherence among individuals on ART. Some of the HIV/AIDS related studies based on HBM constructs conducted in the international health arena used different methods of communication cues to action methodologies, such as drama or song to increase HIV/AIDS knowledge and to remind the participants to adopt safer sexual behaviors (Bosompra, 2007). A qualitative study was conducted to ascertain feasible communication strategies which may influence ART adherence. The authors found that cues to action was one of the constructs that was acceptable and feasible to use to communicate adherence messages with patients on ART (Rochon et al., 2011). Mattson (1999) conducted a study to review the role of persuasive communication cues by HIV test counselors in changes in safe sex behavior of individuals getting tested for HIV. The pre- HIV test results did not show any correlation between the HBM constructs and safe sex attitude among participants. However, post-HIV test results which took place after an HIV test and a persuasive communication session was conducted with the counselor, indicated higher perceptions of susceptibility, severity and improved health behavior attitude. This highlighted the importance of communication cues in affecting knowledge and attitudes among individuals

Starks et al. (2008) conducted a qualitative study at a hospital in Beijing, China to better understand what patients on ART need, to obtain optimal treatment adherence. They hypothesized that four crucial components, which work interactively but result from various factors from individuals' lives, have an effect on ART adherence. These were: (a) Access to ART (a structural factor around availability of ART, (b) Knowledge about ART (cognitive factor around regimen, side effects viral resistance, etc.), (c) Motivation to take the medication (a

psychological factor), and (d) Prompts or cues to remember to take the medication on time (internal or external cues). The study participants raised stigma and discrimination, side effects of ART, cost of lab tests, transportation to the clinic and time away from work as major barriers to treatment adherence. Most of the participants were comfortable with their ART knowledge and knew how the ARTs worked, how to manage side effects, consequences of missed doses, etc. The motivation to take the meds was also high as they were aware of the health benefits of ARVs and they had a strong desire to live longer. The participants used a mix of internal (personal schedules) and external (alarm and electronic tools, or other people) cues to remind them to take the medication. The results from the Starks et al study indicated the acceptability and feasibility of using cues to improve adherence on ART, thus strengthening the hypothesis for this study that the appointment reminders would be effective in bringing about the behavior of appointment adherence in the study population.

Literature Related to Key Variables and Concepts

HIV Epidemic

Sub-Saharan Africa region is the worst hit by the HIV epidemic compared to the rest of the world. Approximately 25 million out of 35 million people globally living with HIV are in this part of the world (UNAIDS, 2012). South Africa ranks as one of the most affected countries, with a national antenatal HIV prevalence of 30%, in a population of approximately 47 million (South African National Strategic Plan on HIV, STIs and TB 2012-2016, 2012). In 2008, 5.5 million people were living with HIV in South Africa and over a million people needed be on ART (Ojikutu et al., 2008). At the end of 2013, 6.1 million people were living with HIV in South Africa (PEPFAR annual report, 2013)

Globally, there has been a surge in access to ART over the last few years with a 20-fold increase in Sub-Saharan Africa (Micek et al., 2009). The South African government rolled out its ART program in 2004. The government with support from international donors, and local and international development agencies has made great strides in enrolling a large number of people on ART in a short period of time. South Africa currently has the largest ART program in Sub-Saharan Africa with over 2.5 million individuals on ART in the public sector as of October 2013 (Ojikutu et al., 2008; PEPFAR annual report, 2013).

Loss to Follow-up

As the ART programs have scaled up, the focus for most countries has moved from initiating patients to retaining them on ART since being on ART is a life time commitment. Once on ART, patients have to strictly adhere to their daily medication regimen, which can be multiple pills at various times during the day, and the patient is required to return to the clinic for follow-up appointments for clinical management and medicine refills (Miller et al., 2010; Ketlhapile et al., 2010). While great achievements have been made in initiating patients on ART, there are concerns about the long-term outcomes in terms of patient adherence and retention in HIV treatment (Barnighausen et al., 2011; Maskew et al., 2007). A systematic review of ART programs in Sub-Saharan Africa showed only 60% of patients still on ART two years after starting treatment (Rosen, et al., 2007). This was similar to the rates found in treatment of other chronic diseases globally. Rosen et al., 2007, found that 25% of patients had dropped out by year one of ART initiation, with this number rising to 40% by year two on ART. Researchers in Malawi found that the median time between initiation of ART and patients stopping follow-up clinic attendance was 4.3 months (Yu et al, 2007). The median time between initiation on ART and first missed appointment at a public sector tertiary hospital serving the inner city of

Johannesburg, South Africa was found to be 84 days (IQR 43-168 days, range 13-392 days) (Dalal et al., 2007).

Rosen et al. (2007) placed the reasons for attrition from ART into four main categories. Death and LTF were the most common followed by patients intentionally stopping their treatment, and patients transferring to other ART facilities without informing their former ART clinic (Rosen et al., 2007). LTF is defined as the disappearance of the patient from the ART program for no reported reason (Rosen & Ketlhapile, 2010). Researchers and countries use different time frames to identify patients as LTF. These can range from 30-90 days past the missed follow-up clinic appointment date (Yu et al., 2007). LTF rates from a multi-site patient file audit at public sector clinics in two provinces in South Africa between 2006 and 2009, were found to be between 14-25%, with the largest proportion of patients becoming lost to the system in the first 6 months of starting ART (Jaffer et al, 2007). A large public sector clinic with over 7000 patients enrolled on ART in Johannesburg had a LTF rate of 16.4% among patients initiating ART between April 1, 2004 and March 31, 2008. Forty percent of the individuals became LTF in the first three months after starting on ART (Rosen & Ketlhapile, 2010).

LTF is the major cause of treatment attrition. Patients who discontinue ART are at high risk of: developing virological failure, acquiring opportunistic infections and early mortality (et al., 2007). Harries et al., 2010, conducted a meta-analysis of sixteen studies in Sub-Saharan Africa and found that between 20-60% of patients who were identified as LTF had died. Researchers in Malawi found that about 50% of the patients who had been identified as LTF had died, most dying soon after they missed their clinic follow-up appointment (Yu et al., 2007). Dalal et al., 2007, conducted a study at an ART clinic in a tertiary government hospital and found that one in six patients initiating ART were LTF. Once again, approximately 50% had died

with a majority of patients dying within 30 days of missing their appointments (Dalal et al., 2007). Some of the reasons found for LTF included ART costs, unavailable transport or transport costs, long waiting times at the clinic, stigma, family pressures, illness, transferring to other ART facilities, and others (Dalal et al., 2007). Health services factors identified for missed clinic appointments included poor communication, poor waiting areas, and duration between appointments. Patient related factors included transportation difficulties, health beliefs and forgetfulness (Kliner et al., 2013). The mHealth intervention that was evaluated during this study was developed to improve communication with patients, reduce waiting times (resulting from patients arriving on the day and time of their scheduled appointment), and reduce appointment forgetfulness among the patients.

According to the South African HIV/AIDS care and treatment guidelines outpatient HIV care program starts at the PHC level. That is, individuals have to get their pre-test counseling, HIV testing and post-test counseling at a PHC. If the individuals test positive, then their blood is drawn to ascertain their CD4 count. It can take between 5-7 working days to receive the CD4 count result. The current standard of care requires the individuals to return to the clinic to receive their CD4 results. ART commencement eligibility is ascertained via a WHO guideline staging and the individual's CD4 count. The current eligibility for immediate ART initiation are as follows:

- Any HIV positive child 0-5 years
- Any HIV positive pregnant woman
- Any HIV positive individual with active TB disease
- Any individual with a baseline CD4 <350 cells/ml^3

If individuals are found to be eligible to start on ART, they are enrolled in pre-ART care, provided adherence and ART initiation counseling, and initiated on ART. The patients are required to return to the clinic once a month for follow-up appointments for clinical monitoring and ARV refills (South African National Strategic plan on HIV, STIs, and TB 2012-2016; South African HIV/AIDS treatment and PMTCT guidelines, 2011 and 2013).

Results from patient file reviews in South Africa have indicated that at each key phase of the clinical cascade, there is a risk of patient attrition (Jaffer et al., 2009). The attrition can happen at two key phases in the clinical cascade. One is the pre-ART and the other is the post-ART phase. Results from retrospective file reviews conducted at public sector ART sites in South Africa indicated between 50- 60% attrition or loss to initiation during the pre-ART phase, and between 14-20% loss to follow up in the post-ART phase (Jaffer et al, 2007). Figure 2, derived from the UNAIDS 2014 report shows that in Sub-Saharan Africa, 45% of individuals who have HIV get tested to find out their HIV status. Of the individuals who are eligible for ART, only 39% get initiated on ART, and retention after ART initiation is under 30%.

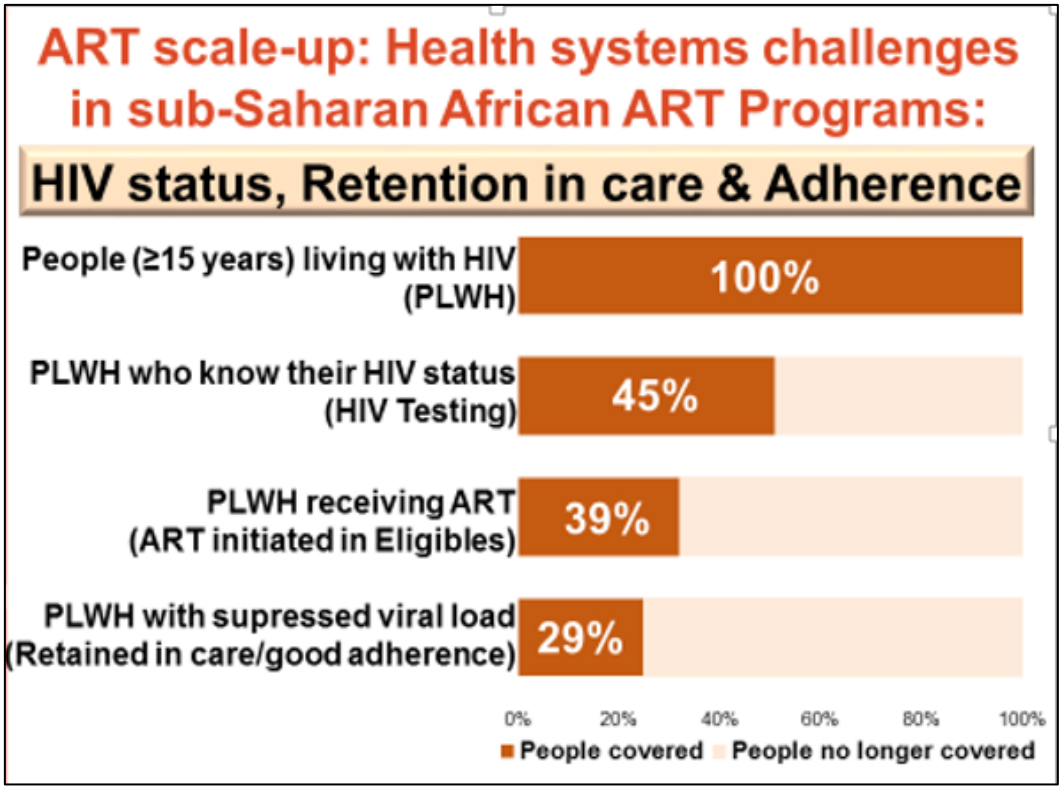

Figure 2. Proportion of HIV positive individuals who get tested to find out their HIV status, initiate on ART and are retained on ART in Sub-Saharan Africa.

Source: UNAIDS Report, 2014; extracted from Abdool Karim, 2014.

Missed appointments and LTF

Regular follow-up clinic attendance is crucial for positive clinical outcomes of patients as the patients receive their ARV refills at the end of the visit. Missed clinical appointments have been found to be a significant risk factor for development of virological failure and AIDS defining illnesses (Lucas et al., 1999; Nyandiko et al., 2013; Rastegar et al., 2003), and death (Park et al., 2007). Viral resistance can develop quickly in an individual with poor adherence to ART. It can occur after 11-30% missed ARV doses (Maskew et al., 2007).

There is evidence in the literature on linkages between repeated missed appointments and low treatment adherence in patients with chronic illnesses (Levine et al., 1987), and between missed appointments and LTF of patients on ART (Jaffer, 2009). Missed appointments also have

negative impacts on health services, as they can increase cost and lower efficiency of service delivery (Guy et al., 2012). Moreover, missed appointments can lead to delays in diagnosis of treatment related side effects or other illnesses, thus delaying timely management of diseases, leading to unanticipated burden on the health system where resources are already limited (Car, Guro-Urganci, de Jongh, Vodopivec-Jamsek & Atun, 2012; Rosen et al., 2007).

Brennan et al. (2010) conducted a retrospective cohort study at one of the largest ART clinics in South Africa with more than 17,000 patients enrolled on ART in 2010. They looked at the relationship between missed follow-up ART clinical appointments in the first six months of ART initiation and the outcome of mortality, LTF, immunologic response to ART, and virological suppression due to ART. The researchers found that of the 4476 individuals who had initiated on ART during the study twelve month observation period, only 65% attended all follow up visits as scheduled. Approximately, 2.6% of the patients had died and 6.2% were LTF. In addition, higher missed clinical appointments were found to be associated with increased risk of mortality and LTF during the study period. Immunologic response was ascertained by improvement in CD4 count compared to the CD4 count immediately before initiation on ART. The researchers found that patients who missed three or more ART or clinical appointments were at high risk of low CD4 improvement. Furthermore, patients with three or more missed ART appointments were at increased risk of not achieving viral suppression by six months compared to the patients who did not miss any appointments. This study was one of the first to look at the relationship between missed appointments early in the treatment phase of patients initiating ART and the health outcomes of the patients, in a resource limited setting (Brennan et al., 2010).

Some of the reasons for missing appointments include forgetfulness, confusion regarding follow-up appointment, relocation, illness, hospitalization, transportation cost, side effects, death

and insufficient medication supply (Dalal et al., 2007; Maskew et al., 2007). Forgetting appointments is a common reason given by patients for missing outpatient clinic appointments in a variety of health care settings (Leong et al., 2006; Guy et al., 2012; Kliner et al., 2013)

Regular clinic visits reflect good retention in care among patients on ART. Retention in care is needed for continued access to ART and appropriate monitoring of side effects, toxicities, and treatment failure (Geng et al., 2010). Good retention also translates into continued social and clinical support. Poor retention in care is reflective of low treatment adherence and treatment cessation. Once treatment is interrupted, the effects of ART can quickly reverse and cause harm to the patients (Geng et al., 2010). Streamlined and active patient tracking has been recommended by some researchers while others have suggested some form of reminder systems which may reduce the rate of missed appointments (Dalal et al., 2007; Kliner et al., 2013). Other researchers have recommended implementing a patient tracer program whereby patients missing their clinic appointments are contacted and asked to return to the clinic in a timely manner (Yu et al., 2007).

Since LTF was highlighted as a critical issue by some key studies especially by Rosen et al., 2007 and Dalal et al., 2007, some countries in Sub-Saharan Africa developed and implemented patient follow-up or tracker programs. Some of the projects involved hiring a social worker or counselor who contacted patients missing clinic appointments by phone or home visits. Other projects used a community based approach, whereby community workers approached the patients identified as LTF (Rosen & Ketlhapile, 2010). Researchers studying the effectiveness of tracer projects have found success in improving patients returning to the facility after being contacted by a tracer. In a Kenya based study, the rate of return of patients was found to be 65% and 49% in urban and rural areas respectively (Rosen & Ketlhapile, 2010). The

researchers of this study also examined the cost effectiveness of a patient tracer project. They found that the average cost of returning a patient to the clinic was $432/year. This was equivalent to the cost of almost one year of the first line ART regimen for one person. The researchers questioned that in an environment of reduced donor funding and resource poor settings, is it appropriate to spend this much money to return a patient to care when there are patients waitlisted to initiate on ART? The researchers later suggested using a junior tracer person and also indicated that the cost would reduce to $18 if the cost of the patient tracer project was distributed among all patients accessing ART services (Rosen & Ketlhapile, 2010).

While a patient tracer program has been found to be an effective and useful intervention, it can be resource intensive based on patient load per tracer, and follow-up workers' salaries, transportation and communication costs. Therefore, there is ongoing search for alternative ways of tracing or communicating with patients to assist them with maintaining good appointment adherence and retention in care. The intervention evaluated in this study used a low cost way of communicating with patients on ART to promote clinic appointment adherence. No studies were found in the peer reviewed or grey literature that examined the association or effectiveness of SMS on improving ART clinic appointment adherence among patients receiving ART services in South Africa. Additionally, improving retention in HIV care and treatment by reducing LTF are priority areas for the South African Department of Health (South African National Strategic Plan on HIV, STIs and TB 2012-2016, 2012). The department is looking for solutions to improve long-term retention in care of patients on ART, following the huge success of initiating over 2.5 million people on ART in the last ten years.

Mobile Health technology to improve health services

Mobile technology includes cell phones, patient monitoring devices, personal digital assistants, and other equipment. (Bahadur & Murray, 2010). mHealth applications range from communication between health care provider and patient, delivery of services, patient education, data collection at point of care, disease outbreak monitoring and reporting, training of health workers in remote settings, HIV medication and treatment adherence support, and appointment reminders. (Rodrigues et al., 2012; Tomlinson et al., 2013). The methods of communication with cell phones include: text messaging or SMS, voice messaging, phone calls, World Wide Web based social media platforms, Unstructured Supplementary Service Data (USSD), and smart phone applications.

mHealth is a rapidly growing field. It is increasingly being used to improve delivery of health services in both resource limited and rich settings (Leong et al., 2006; Peron et al., 2010). mHealth is considered to have a great potential for strengthening health service delivery and leading to positive health outcomes especially in resource poor countries (Free et al., 2013). The acceptance of cell phones and their low cost has led to the quick uptake of mHealth technology in health services (Rodrigues et al., 2012). One of the main reasons for mHealth popularity and growth is a result of the extensive cell phone penetration globally. In 2009, more than four billion or two-thirds of the world's population owned cell phones. Over 60% of these phones were in developing countries or emerging economies (Free et al., 2013; Bahadur & Murray, 2010). In most developed countries, there are more cell phones than the population. In developing countries, mobile phone is the fastest growing communication sector. This is due to poor infrastructures for landline phones, greater mobility with cell phones, easier access, low startup cost, flexible payments, relatively low cost of communication especially as it pertains to

text messaging, access to the Internet, Unstructured Supplementary Service Data (USSD)- a widely used mobile communication technology between the phone user and mobile network, and other modes of mobile communications (Bahadur & Murray, 2010). Eighty percent of the world's population lives in areas with an active mobile phone network thus making mobile phone technology a viable option for reaching a large number of people (Bahadur & Murray, 2010).

mHealth has great potential for success in South Africa as the country has one of the highest proportions of mobile phones per capita, with over 90% of people having a mobile phone subscription (Leon et al, 2012). The rural and remotest parts of the country also have high cellular network coverage (Crankshaw et al., 2010). The South African Government has shown a keen interest in the use of mHealth technology in the public health care sector. In 2012, the National Department of Health (NDoH) circulated a comprehensive eHealth strategy which included the need for development, implementation and evaluation of mHealth interventions to strengthen the public health sector (NDoH eHealth strategy, 2012). In addition, there is growing interest and support by the United States government, the World Health Organisation, multinational companies and other private entities such as the cell phone network providers to develop, implement and evaluate innovative mHealth interventions to help strengthen the South African government's response to the HIV epidemic. This is evident from the increase in funding these agencies have been making available in South Africa over the last 2-3 years. Studies exploring the feasibility and acceptance of using mHealth in the South African population have indicated a high level of interest and acceptability (Crankshaw et al., 2010).

The project evaluated by this study used mHealth technology via SMS to strengthen ART follow-up appointments and thus reduce LTF in public sector facilities. The project was piloted

between November 2011 and October 2012 at a primary health care facility based ART clinic in the inner city of Johannesburg with approximately 2000 patients enrolled on ART. Following the positive outcomes of the pilot, there was a request by the funding agencies and the DoH to scale up the SMS for ART appointment reminder at a larger secondary level community health center in the inner city. This facility, Hillbrow Community Health Center (HCHC), had over 16,000 patients enrolled in ART at the time of program implementation. This is one of the largest ART sites in Sub-Saharan Africa serving South Africans and a large number of immigrant and hard to reach populations such as sex workers, pregnant women, and others. The ART clinic (WARD 21), at HCHC was started in April 2004, when the NDoH rolled out the national ART program. A patient file audit was conducted in 2008 to ascertain the patient outcomes at the facility, four years post ART roll out. This site had similar issues of patient LTF, as noted earlier in this chapter. Historical clinical and loss to follow up data from Ward 21was used in the study. This information, along with the project and retrospective patient clinical data provided an appropriate evidence base to draw conclusions from.

SMS Related Interventions in HIV Care and Treatment

SMS or text messaging is a well-established technology, which is recognized and utilized around the world. It allows a person with a cell phone to send a short message, about 160 characters, to another person on their cell phone. The message delivery is immediate if the recipient's phone is switched on and in a network area. The recipient has the option to respond immediately or wait. SMS is a cheap and efficient method of two way communication which costs much less per text message versus per minutes expenses for a cell phone call (Leong et al., 2006; Bahadur & Murray, 2010).

Over the last few years, SMS has been identified and used as the most prevalent mHealth technology application. Bahadur and Murray (2010) conducted a literature review between February and December 2008, to examine the use of SMS in health care settings. Out of 212 articles and reports reviewed, 28 were found to meet the study criteria. The authors found studies which indicated that SMS had: improved service delivery through appointment reminders, improved communications between health care workers, increased: diagnosis, prevention, adherence to treatment, treatment monitoring, contact tracing, and others. The authors concluded that most of the studies were conducted in developed countries. SMS was found to be an efficient, cost effective and appropriate technology for strengthening various health services sectors. However, Bahadur and Murray noted that some researchers were skeptical about the evidence around the effectiveness of SMS since many of the reports or articles generated were from pilot projects or feasibility studies versus rigorous enquiry. The authors concluded that while SMS has been found to be effective in the public health sector, there is a need for further rigorous review of the benefits of this technology to improve health services in South Africa (Bahadur & Murray, 2010). In addition, none of the studies reported by Bahadur and Murray pertained to use of SMS to improve ART clinic attendance. This is where this study was important. Retrospective clinical and program data from the appointment reminder intervention was used to examine the effectiveness of SMS technology in reducing LTF in the public sector in South Africa.

Acceptability and Feasibility of Cell Phone Use in HIV Care and Treatment

In the last five years there has been a growing interest in the use of SMS technology to strengthen the HIV/AIDS health services sector. Chib, Willkin, Ling, Hoefman & Biejma, 2012 conducted a study in Uganda in 2009 to look at the effectiveness of an incentive based

HIV/AIDS health education intervention using SMS to: increase knowledge around HIV/AIDS, improve awareness among the participants about their local HIV testing facilities, advocate HIV Counseling and Testing (HCT), and increase uptake of HCT among the participants. The messages in the form of thirteen multiple choice and true/false questions were sent to 10,000 mobile phone subscribers with the help of the local telecommunication company, over a one month campaign period and in one district. The information was provided by "Text to Change", a Dutch not for profit organization which provides health education services via mobile phones, in Africa. The questions pertained to: HIV/AIDS knowledge, testing, and HCT services in the area. The subscribers were given an option to opt out, however, none did. Subscribers, who answered the questions correctly, received a free HCT service and were enrolled into weekly drawings for free mobile phones or airtime. The authors reported that 233 out of 10,000 (2.3%) subscribers accessed HCT services at the local clinic during the campaign period. This paper only examined HIV knowledge among the subscribers as the researchers did not collect data to look at association between the campaign and testing behavior. Approximately a quarter, 2,363 of the 10,000 people who were sent messages responded. Of these, 1,954 answered the quiz questions with most people only answering one or two of the questions. Thirty individuals answered all thirteen questions. On an average, the respondents got 68% of the questions correct. The researchers only looked at existing HIV knowledge versus changes in HIV knowledge. Only the subscribers who answered the questions were provided with the correct answers. While the researchers set out to look at correlations between SMS and service uptake, they did not collect the relevant data to answer the question. This type of a study design also indicates the limitations of blast messaging to the subscribers. The researchers indicated limited success and recommended making SMS a constituent of an integrated mass media campaign versus a

standalone intervention, one should question if the study design had an impact on the results. (Chib et al., 2012).

Apunyu and Hoefman (2010), who were co-authors on the Chib et al., (2012), study conducted another study in a different district in Uganda in 2010. The aim of the study was similar to the previous one; however, the study methodology was different. The researchers used a survey methodology using "Text to Change" services. Information regarding the survey was broadcasted via radio talk shows on two radio stations serving the district followed by short radio messages broadcasted seven times a day (five times in the local language and twice in English), to encourage people to participate. People were informed that they could opt in to participate in the survey by sending a SMS to a toll free number. Additionally, flyers were distributed in the main town and community health workers collected phone numbers face to face. As with the previous study, participation in this study was incentivized. 8272 individuals subscribed to participate in the study. Of these, 1,222 did not respond to any SMS messages. Therefore, analysis was done on the remaining 7,050 participants. Fifty three-percent of participants answered the HIV knowledge and family planning questions. Over 50% of respondents answered an average of 74% of question correctly. More women answered correctly versus men ($p < .001$). The AIDS information Centre located in town also offered free HCT during the survey period. The center noticed a momentary increase in HCT uptake after announcement of free testing. Eighty percent of the initial respondents had heard about the survey by radio. Ninety six percent of the participants stated that they had improved their HIV knowledge from participating in the survey. The researchers did not conduct a pre and post study so one does not know if there was an actual change in HIV knowledge. The authors mentioned that the participants had a relatively higher HIV knowledge compared to the national average (ascertained by national surveys). They

also stated that the SMS survey was highly valued by the participants and the acceptability was high. The AIDS information center had an increase in HCT uptake however; the authors did not provide information differentiating the survey participants from the general population. There was a high acceptability of the SMS survey and a large number of the participants indicated that their HIV knowledge increased however, the authors do not provide any evidence showing a correlation between the intervention and increase in HIV knowledge and HCT uptake among the participants. One should also consider the possibility of participant bias on the outcomes noted.

A group of researchers conducted a cross sectional study to examine the use of and feasibility of cell phones for ART clinic appointment reminders and adherence messages in Durban, South Africa (Crankshaw et al., 2010). Primary analysis was on the existing patterns of cell phones and willingness to be contacted by the clinic, by gender. Three hundred individuals over eighteen years of age were enrolled in the study between October and December 2007, from an ART clinic located in an urban/peri-urban state subsidized district hospital. Approximately 81% of the participants owned a cell phone. The female (67%) to male (33%) proportions among the participants was similar to the gender proportions of individuals accessing services at the clinic. Over 60% of the participants were unemployed and more than 52% had a secondary level education. Approximately 41% of the participants had been on ART for less than six months, followed by 26% and 33% for 7-12months and more than 12 months respectively. The researchers found that regardless of gender, 99% of the participants were willing to receive phone calls from the clinic, and 96% were willing to receive text messages. However, while the participants considered the reminders as useful, they did not consider it critical to the success of their treatment. Significant gender differences were found for questions pertaining to patterns of cell phone use. More women: switched off their phones during the day ($p = 0.002$), sometimes

did not take phone calls in certain places ($p < 0.0001$), shared a phone with someone ($p = 0.002$), and left the phone sometimes where someone could pick it up and read the messages ($p = 0.005$). Most of the participants stated using the cell phone alarm to remind them to take their medications. The researchers also found other factors, which they mentioned, should be considered when designing mHealth interventions. These included items such as theft or damage to cell phones, which could affect long-term sustainability of the project and may affect participant confidentiality. A solution to the sustainability issue was to update the contact details at each clinic visit. Another issue highlighted was the unavailability of the participant to receive the call. Text messaging was found to be more viable as the messages could be accessed by the participants any time. Another point raised was the need to involve the patients when developing the messages. This study had several advantages in that it involved a representative sample of patients accessing ART in a high HIV prevalence area in South Africa. The researchers found that the participants were similar as far as time on ART and gender breakdowns were concerned. Disaggregation of the data by gender highlighted hidden nuances that can impact the outcome of an appointment reminder intervention. Some of the limitations of this study were that the information was based on responses from the participants. Actual behaviors associated with the use of cell phone were not ascertained. As the researchers mentioned in the article, there could be some degree of courtesy bias for willingness towards reminders. This could have overestimated the positive response noted. There is also a possibility of recall bias for responses to cell phone use questions. In addition, the authors caution the readers against generalizing the results to other populations. The clinic where the study took place has a small fee for ART services. This is different from other public sector clinics where services are provided free of charge. The clinic may be supporting populations with some socio-demographic differences compared to the

population receiving services at public sector clinics. In conclusion, the authors found a high acceptability of appointment reminders in South Africa, and highlighted the importance of conducting acceptability and feasibility studies prior to development and implementation of interventions.

The three studies reported above show varying levels of acceptability for cell phone calls or SMS in HIV care and treatment. The Apunyu and Hoefman (2010) study highlighted the advantage of individuals opting in to participate in an activity versus the Chib et al. (2012), study which used blast messaging to enroll individuals. Crankshaw et al., (2010), showed the need for formative studies prior to development and implementation of interventions. The appointment reminder intervention that was evaluated during this study was developed using a project development cycle. The intervention was developed following a focus group based acceptability and feasibility study in the target population. The participants were asked about acceptable SMS content too. The intervention was piloted for a year at a primary health care based ART clinic and then rolled out to the current ART clinic, which provides free services. People accessing services at the clinic were approached by program staff and enrolled after a consent process. Informal process evaluations were undertaken over the last two years to ascertain appropriate implementation of the planned intervention. An outcome evaluation was the next relevant step in the project's development cycle. It ascertained if the intervention was effective in improving adherence to clinic appointments and reducing LTF among patients on ART who received the appointment reminder intervention versus a comparison group, which did not receive the intervention.

SMS to Improve Adherence on ART

As mentioned earlier, patient adherence to ART is crucial for continued benefits of ART in avoiding development of viral resistance, reducing opportunistic infections, and early mortality (Rosen et al 2007). In addition, adherence to ART has been linked to improved health outcomes and is important to contain undue program costs (Lester et al., 2010). According to Pop-Eleches et al., (2011), it is important to prevent adherence related treatment failure, especially in resource constrained settings as the cost of second line regimen can be up to 17 folds higher than the first line regimen, that is, if the second line regimen is even available in the country. Since adherence is crucial for ART success, a number of interventions have been developed and implemented over the last few years. These have ranged from direct administration of ART, provision of financial incentives, education, additional counseling regarding adherence, facilitation of social support, and electronic and phone reminders (Rodrigues et al., 2012). In the last 3-5 years, a handful of studies exploring the use of SMS in improving ART adherence have been published.

Lester et al., 2010 conducted a Randomized Control Trial (RCT) in Kenya between May 2007 and October 2008 to study the effectiveness of SMS on ART adherence. According to the researcher, this was the first clinical trial to report use of mHealth in improvement of clinical level outcomes in patients on ART. This trial is seen as a landmark study in the field of HIV/AIDs and mHealth. The trial was conducted at three ART clinics, involving 538 patients who were equally randomized to the intervention or the control group. The intervention group received weekly SMS messages from the clinic nurse with a simple question asking how they were. The participants were supposed to respond within 48 hours if everything was OK or if there were problems. If the response mentioned “problems”, then the nurse called the

participants to inquire. The control group received the standard of care. The primary outcomes of interest were self-reported ART adherence at the 6 and 12 months follow-up visits, and viral load suppression at twelve months. Secondary outcomes included attrition at twelve months due to death, transfer to other non-study clinic, withdrawal from the study or loss to follow up. The researchers also examined differences on outcomes noted by gender, type of residence (urban or rural), disease staging, phone ownership and others. One of the major strengths of this study was the review of the viral load at twelve months. While self-reported adherence is the most commonly used method of ascertaining treatment adherence, there is a high risk of reporting bias. In this study, the participants were considered adherent if they mentioned taking more than 95% of their prescribed pills in the thirty days prior to their six and twelve month visits. Viral load ascertainment requires a blood draw and it indicates the actual viral count in the blood. According to Lester et al., (2010), "viral load is an important composite endpoint for monitoring adherence and takes into account pharmacological, biological and socio-behavioral factors." In this study, viral suppression was 400 copies per mL or less at the twelve month follow up. Participants with more than 400 copies per mL were classified as having virological failure. The study was powered to note a 10% improvement from baseline, between the two groups. The researchers found that significantly more patients in the intervention group reported adherence of > 95% ($p = 0.006$) versus the control group. The difference was significant even after adjusting for baseline covariates ($p = 0.0028$). In addition, more patients in the SMS group had suppressed viral loads of < 400 copies per mL at twelve months ($p = 0.04$) versus the control group. After adjustment, there was weak evidence of improved viral load suppression in the intervention versus the control group ($p = 0.058$). There were no significant associations with the secondary outcomes. At the end of the study, 98.5% of the participants in the intervention arm wanted the

intervention to continue, and 98% mentioned that they would recommend the SMS intervention to a friend. Many patients mentioned that they felt “like someone cares”. Results of this study showed that mHealth interventions can improve clinical health outcomes of patients on ART and participants found the intervention valuable. The researchers also mentioned that the SMS intervention was inexpensive as each SMS message was USD 0.05 which totaled $20 per month for 100 people. The calls per care providers averaged $3.75 per month indicating that the interventions can include a human touch at a low cost. The researchers further indicated that based on these statistics, this intervention may have been cheaper than the cost of a community adherence intervention, which involves individuals to make home visits and requires travel and personnel time. The authors also presented a hypothetical example for scale up of the intervention in Kenya using the example of close to 300,000 individuals who received ART in 2009, supported by U.S. government funding. They estimated that if the SMS intervention was scaled up in 2009, approximately 26,000 additional people could have had fully suppressed viral loads (Lester et al., 2010).

Another study conducted in a rural setting in Kenya examined the correlation between SMS and ART adherence (Pop-Eleches et al., 2011). The RCT was conducted at a single public sector rural health clinic between June 2007 and August 2008 with 720 participants. All the participants were provided with a mobile phone with basic features, and they were told to use the phone as they wanted. However, the participants were asked to bring the phones to the monthly follow-up visits. A replacement phone was not provided if the participants lost or damaged the phone. The participants were also asked to take one of their three ART regimen medications to the pharmacy, where the medication was transferred to a container with a medication event monitoring system (MEMS) cap, which captured information on the number of times the

container is opened. A third of the participants were randomly assigned to the control group, which did not receive any SMS messages. The remaining participants were randomly but evenly allocated to one of the four intervention groups. The four interventions were based on four different types of short and long one–way SMS reminder messages based on adherence barriers identified by other studies. The barriers included forgetfulness and social support issues. The short messages just reminded the participants to take their medications while the long messages provided some supportive language. The participants had to return to the clinic on a monthly basis to get their MEMS cap recording. The researchers gave money to the participants to pay for charging of the cell phones at public charging stations as there was poor access to electricity and most participants could not afford it. In addition, small amount of money was added on each phone every two months. The study was powered to detect a 15% difference between the intervention and control group. Adherence was measured based on a proportion of number of actual container opening over prescribed opening over a 12-week period. The primary study outcome queried was adherence of > 90%. Secondary outcome included treatment interruption of greater than 48 hours (ascertained by MEMS opening), during each analysis period of twelve weeks. Baseline demographic information was similar among all participants. Approximately 16% of the participants were lost to follow up at the end of the study with no significant difference in the loss to follow up rates between the four intervention and control groups (p = 0.48). The study results showed that the patients receiving weekly reminders had a higher likelihood of achieving 90% adherence to ART – almost 13-16% higher compared to the control group that did not receive any reminders. The control group had a drop in adherence from 60-46% over the 48 weeks of observation. Instances of treatment interruptions of more than 48 hours were also lower in the group that received the weekly reminders. The investigators did not

find a difference in the effectiveness of the longer or shorter text messages in improving the ART adherence. The investigators also found that while the group receiving the weekly reminders had improved adherence, this was not the case with the group receiving the daily reminders. One of the reasons provided for the reduction in effect was "Habituation" i.e. the possibility of over stimulus. The researchers concluded that they had provided robust evidence that SMS reminders may improve ART adherence in resource constrained settings, and the low cost of setting up the system and sending SMS may be beneficial in these types of settings. Pop-Eleches et al., further stated that their study was one of the first with evidence of the beneficial effects of mHealth in the field of HIV care and treatment and suggested the need to test it in other areas in the field such as appointment reminders, treatment side effects and other communications between the patients and their care providers (Pop-Eleches, 2011).

Rodrigues et al. (2012), conducted a quasi-experimental cohort study in India between 2010 and 2011 to examine the effects of weekly mobile phone reminders on adherence to ART in the short term (6 months) and long term (12 months). Interactive Voice Response (IVR) and SMS technologies were used in this study. The cohort included individuals who were (a) HIV infected adult patients followed up as outpatients at the clinic, (b) had access to a cell phone, (c) had been initiated on ART for at least a month at the time of enrollment in the study, and (d) on the first line ART regimen. The intervention had two components and it was provided to all the participants, once a week for six months. The first component was an interactive IVR call with one question that the participants had to respond to. The question was "have you taken all your medicines yesterday?" The second component was a non-interactive SMS, which included a simple picture of a lamp and did not have any text. The participants were trained to respond to the IVR and access the SMS message. One hundred and fifty individuals enrolled in the study.

The researchers collected general demographic and some clinical marker information such as baseline CD4 count, regimen type, duration on ART and other. Retention in the study at month 12 was found to be high at 94%. The results indicated a positive effect of the intervention on adherence. The participants gave forgetfulness as the most common reason for non-adherence however, this reduced significantly between baseline (17%), one month (10%), three months (6%) and six months (3%) *(p*< .001). The participants preferred IVR (34%) to SMS (11%), however, a larger portion preferred both methods (44%) ($p < .001$). There was significant improvement in adherence over time, 85% at baseline to 94% at twelve months ($p = 0.016$) for individuals falling in the "adequately adherent" category at each time point. While this study indicated an improvement in adherence, it was reported by the participants, which can be biased (Rodrigues et al., 2012).

The last three studies indicate a positive correlation between SMS messages or reminders and treatment adherence using various ways of measuring adherence. As mentioned earlier in the chapter, loss to follow up rates among patients initiating ART in South Africa are high (Jaffer et al., 2007; Rosen & Ketlhapile, 2010). In addition, missed clinic appointments are linked to reduction in treatment adherence among patients on ART (Levine et al**,** 1987; Rosen et al., 2007; Car et al., 2012). Therefore, it is imperative to improve ART patients' attendance to ART clinics (Pop-Eleches, 2011). However, no studies were found during the literature search which were based in Sub-Saharan Africa, and which had examined the effects of SMS reminders on ART clinic appointment adherence and LTF. This study provided the evidence needed. In the study, LTF outcomes at six and twelve months were compared between the intervention and the comparison groups. The intervention group comprised of all individuals on ART who had enrolled in the appointment reminder intervention between September 1, 2012 and February 28,

2013. The comparison group was selected from the clinic population that had not enrolled in the appointment reminder intervention. A partly purposeful, partly random stratified approach was used to align the comparison and the intervention group. The standard of care provided to all the individuals remained the same, and the health providers were not aware of who was and was not enrolled in the intervention. The intervention was planned such that the group received appointment reminders three times between their clinic appointments (usually 30 days); one message two weeks before and one a day before the scheduled appointment, followed by one message the day after the appointment. The first two messages were simple reminders that the person has an appointment on a particular date. The third message varied based on if the patient showed up for their appointment. If they showed up then they received a message thanking them and information for the next appointment was included. If they did not attend the clinic then the message urged them to return to the clinic as soon as possible. The evaluation of this intervention was sufficiently powered to provide evidence if the SMS reminder was effective in improving the desired behavior of clinic attendance and ideally lower LTF rates.

SMS for Clinic Appointment Reminders

Due to the lack of studies in the literature which examined use of SMS technology to improve ART clinic attendance, especially in resource limited countries, the literature search included review of studies which pertained to use of SMS for appointment reminders in a number of health care settings in resource rich and limited countries. The search was focused on use of SMS in outpatient clinic settings because ART services in South Africa are often offered in outpatient settings.

One of the earlier studies on use of text messaging to improve primary clinic attendance was conducted in Malaysia by Leong et al., 2006. The study was a three-arm multicenter

randomized control trial with a total of 993 participants. The primary hypothesis was that text message reminders were more effective than no intervention in improving primary clinic attendance. Secondary hypothesis of the study was that text message reminders would be more cost effective than the cell phone calls. The trial took place at seven primary health care facilities (five private and two public). The three arms were text message reminders, mobile phone call reminder, and no reminders. In both the intervention arms, a reminder was sent around 24-48 hours before the clinic appointment and the messages were kept similar. The researchers had a strict definition for non-attendees. Any participant who did not come to the clinic on the day of the appointment was marked as a non-attendee. If the participants came earlier or on another day, changed the appointment date, cancelled or did not come at all for their appointment they were marked as non-attendees. The attendance rate of the individuals in the text message reminder group was significantly higher (59%) versus the control group (48.1%, $p = .005$). Similar rate was found for individuals who received a cell phone reminder (59.6%) versus the control group (48.1%, $p = .003$). However, there was no significant difference between the groups receiving the text message versus the group receiving phone reminders ($p = .874$). The researchers also found that while there were significant differences between the intervention and control groups, approximately 40% of the participants were classified as non-attendees. A reason for this high non-attendee rate could be due to the strict definition for non-attendees. Close examination of the data reveled that about 48% of the attendees did not come to the clinic on their appointment days, but they did return on another day. The authors also found that text messaging was much cheaper than the cell phone call. In conclusion, both the text message and phone reminders were found to be more effective versus no messages and the text messages were more cost effective than the cell phone reminders.

Another study was conducted in Kenya by Odeny et al., (2012), to measure the effectiveness of text messages on improving the seven day follow-up appointment rate for patient undergoing a male circumcision procedure. According to the researchers, this was the first randomized control trial which looked at the outcomes of SMS to improve clinic attendance in a resource limited country. Male circumcision has been found to be effective in lowering the risk of men acquiring HIV (Gray et al., 2012; Weiss, Quigley & Hayes, 2000). It is a recommended procedure by the World Health Organization (WHO) and Joint United Nation Programme on HIV/AIDS (UNAIDS), which is being adopted by various countries (WHO/UNAIDS 2011). Circumcision is a simple procedure, however there is a risk of development of postoperative adverse events (Muula, Prozesky, Mataya & Ikechebelu, 2007). A seven-day post procedure appointment is standard of care and it is important as the health care providers can monitor the healing process, development of any adverse events, and reinforce postoperative care. However, the seven-day clinic attendance rates are low in many countries (Odeny et al., 2012). The trial was conducted in a large district in Kenya that had an average baseline seven-day follow up rate of 43%. For this trial, men were approached during their post-operative recovery period. A total of 1200 men were enrolled between September 2010 and April 2011 and equally randomized to either the intervention (SMS) or the control group (no message). The text messaging was one-way (researchers to the participants), except for the initial SMS, which the participants were asked to send to the research team at the time of enrollment in the study. The participants were reimbursed for this SMS. Individuals in the intervention group received a SMS each day for seven days at the participant selected time and language. The participants were counted as attended the seven-day postoperative appointment as long as they attended within three days before or after the scheduled appointment date. The study was

powered for a 9.5% change in the attendance rate (43% to 52.5%). Outcome data was available for approximately 99% of individuals in both the intervention and the cohort group. Overall, 62.5% of the participants returned for their follow-up appointment. Further analysis indicated that the rate of return although modest, was significantly higher in the intervention (65.4%) versus the control group (59.7%) (RR1.09, 95% CI 1.00-1.20; $p = 0.04$). Secondary association such as distance to clinic and follow up attendance rate was found to be significant. Association between education level and follow up rate was also noted however it was not significant. The authors discussed limitations in terms of lack of generalizability as they had to exclude almost 49% of the individuals initially screened as they were younger than 18 years. Individuals who did not have cell phones with them at the time of enrollment or who did not own a cell phone were also excluded from the study so it is not possible to compare between the group of people who did or did not have a phone as data was not collected on the latter group. The authors pointed out that the intervention arm still had over 30% of the patients who missed their appointment, even after receiving a SMS. This phenomenon has been noted in other studies, including the Leong, 2006 study described above. The authors noted the need for studies, which would query into the reason for participants missing appointment in the intervention arm. The text messaging was found to be cost effective and not human resource intensive once the individuals were enrolled in the study as thousands of pre-programmed messages were sent out electronically. This would support scale up of this intervention to a larger population.

Guy et al., 2012, conducted a meta-analysis of published and unpublished studies, which presented outcomes comparing appointment attendance among patients who had received SMS reminders and those who had not. The researchers looked at overall clinic attendance outcomes stratified by study design and level of health care facility (primary, secondary, tertiary). Eighteen

studies met the review criteria, of these eight were RCTs and ten were controlled observational studies. All of the studies were conducted prior to 2010. The primary outcome of the studies was the attendance rate, which was the proportion of patients in the intervention and control arms, coming to the clinic on their appointment date. The studies pertained to clinical program areas such as outpatient clinics at hospitals and primary health care facilities. Services included pediatric, ophthalmology, orthodontics, and preventive health. The final group of studies for the meta analysis did not include ART or HIV/AIDS services. Most of the studies (13 of 18) sent generic SMS reminders. Three of the studies used personalized messages and two did not specify. The SMS reminders were mostly sent less than 24 hours (n = 10) prior to the appointment, a few of the studies sent the reminders 24-48 (n = 3) and more than 72 hours (n = 4), prior to the appointments. Analysis showed a high (> 94%) heterogenicity among the observational trials ($p < .01$), versus RCTs, which had 0% ($p = .84$) heterogenicity. Therefore the meta-analysis was restricted to only the RCTs. The researchers found that the SMS intervention in RCTs increased the likelihood of patients attending their appointment by 50% versus the control groups which did not receive any reminders. This was found for all the services areas. The authors concluded that there substantial evidence that SMS reminders may improve attendance rates in a variety of health care settings and thus may be a viable technology to improve health services.

A randomized control trial was conducted at a clinic in Geneva between April and June 2008, to ascertain the effectiveness of patient reminders on missed appointment rates and to get a demographic profile of the individuals missing appointments. 2130 patients were part of the trial. The researchers used a "sequential reminder intervention" for the treatment group, using three modes of reminders starting at 48 hours prior to the clinic appointment. The first mode of

appointment reminder was phone call either to a land line or a mobile phone, followed by SMS or text message if there was no answer to the phone calls after three tries, and finally sending a postal reminder if the participant did not respond to the previous two mechanisms or did not have a land line or a mobile phone. The control group did not receive any reminders. The researchers reported that the intervention led to an overall significant reduction in the rate of missed appointment from 11.4% to 7.8%. Subgroup analyses indicated that the reductions noted were only significant in the general outpatient and smoking cessation appointments. They were not significant in the HIV and dietician clinics (Perron et al., 2010).

Kunutsor et al. (2010), conducted a cross-sectional and prospective study at two rural sites in Uganda to ascertain access to and use of cell phones and assess the feasibility of SMS or cell phone calls to improve clinic attendance among patients on ART and ultimately adherence to ART. The researchers identified and approached individuals attending the ART clinic. They conducted a survey on a random sample of 276 people. Of these 176 individuals had access to a cell phone (either they owned one or were using their friend or relative's), and agreed to be contacted for the study purposes. These individuals also met the study eligibility criteria which included 18 years and older and had been on ART for at least three months. Structured questionnaire was used to collect the baseline information on participants, which included, social, demographic and basic ART treatment data, access to cell phone and extensive questions on the patterns of phone use. Study participants were prospectively followed up for 28 weeks to ascertain if they attended their ART refill appointment every four weeks. Participants missing their appointments were contacted immediately by SMS or cell phone call – based on the method, the participant had chosen, and reminded to attend their appointment. Participant adherence to ART was also calculated every four weeks via a pill count and rated as "optimal" if

found to be 95% and up, and “sub-optimal” if less than 95%. A total of 560 appointments were scheduled during the study period. The clinic visits were classified as “on schedule”, “early” or “missed”. The rate of attendance was 85%, 4% and 11% respectively. Fifty participants had missed their scheduled appointments during the study. Forgetfulness was the highest reason for missing appointment followed by illness, having enough medication, financial and travel issues, and confusion over the appointment dates. The participants predominantly chose to receive a phone call versus SMS due to inability to read the messaged resulting from illiteracy or language issues. Forty (80%) of participants who missed their appointment returned to the clinic after the phone call. The average return time was 2.2 days. Four (8%) of the participants had transferred out, died or classified as loss to follow up. Six (12%) of participants did not return to the clinic. Reasons cited by these individuals included financial constraints or being too sick to attend. Mean treatment adherence level differences pre and post phone call were found to be statistically significant. The researchers concluded that the use of mHealth technology, in this case, cell phone calls were found to be effective in improving clinic attendance and there was high acceptability for this type of an intervention in a resource limited setting. They acknowledged that other studies in developed countries found SMS to be effective however, in the rural Uganda setting, cell phones were preferred. While this study provides evidence of feasibility and acceptance of mHealth intervention to improve clinic attendance and adherence to treatment, it lacked a control group. Also, the researchers did not collect information on whether the patients would have returned to the clinic without the call. Generalizability to the rest of the Ugandan population is questionable too. The researchers suggested a need for a RCT to determine if the outcomes noted in this study could be replicated in other resource limited countries.

Based on the outcomes of the studies included above, there is reasonable evidence that SMS are well accepted and effective in improving clinic appointment outcomes in various health care services settings. The evaluation of the appointment reminder intervention provided evidence on the effectiveness of using text messages in improving clinic attendance and thus lowering the LTF rates among patients on ART at a busy public sector ART clinic. Retrospective clinical and intervention data was used in this study.

Summary and Conclusion

Results from various studies conducted globally have highlighted LTF and retention in care as major threats to the effectiveness of ARVs in controlling the replication of the virus in HIV positive individuals, and the success of the ART programs. Need for innovative solutions and interventions to control these issues have also been identified by various stakeholders. There are numerous published articles on the use and effectiveness of mHealth technology in improving health services in developed countries; however, there are not a lot of studies in the developing country context. Furthermore, there is a gap in the literature on program effectiveness studies pertaining to use of SMS, particularly looking at health related outcomes (Chib et al., 2012), especially in the field of HIV/AIDS. Authors have stated in numerous articles that many of the mHealth studies were based on pilots and lacked rigorous enquiry. Apunyu and Hoefman (2010) go as far as to say that many studies present anecdotal evidence, and they lack sufficient grounded evidence when discussing effectiveness of the interventions.

This study evaluated a mHealth appointment reminder project underway since September 2012 at a large public sector ART site in Johannesburg, South Africa with over 16,000 patients enrolled on ART. The evaluation queried if appointment reminders sent via SMS were effective in reducing missed appointments among individuals enrolled in the intervention versus

individuals not enrolled in the intervention. The 6 and 12 months LTF rates between the two study groups were the key outcomes of interest in this study. The appointment reminders also acted as cues to action for the participants. The effectiveness of the cues in leading to the expected behavior was reviewed during the evaluation.

As mentioned earlier, improving patient retention in care is a priority for the South African NDoH. The appointment reminder project was one of three mHealth interventions implemented in Johannesburg. The NDoH has been informed about these projects and the evaluation outcomes will be shared with the government for possible integration in the national strategy to improve retention in ART.

The next chapter includes information on the rationale for the study design, which was developed in line with the gaps identified during the literature search and the recommendations for future query by the various researchers. The research methodology is tailored to maximize the data available, given the retrospective nature of the evaluation, the intervention design and historical LTF data information available from the clinic.

Chapter 3: Research Method

Introduction

The purpose of this study was to evaluate the effectiveness of a mHealth ART appointment reminder intervention to improve retention in care of patients on ART at a large public-sector ART clinic in Johannesburg, South Africa. This chapter provides a review of the study research methodology. It starts with the research design and rationale section, which includes a description of the mHealth intervention. This is followed by information on the study research design, variables that were analyzed to respond to the research questions, the research methodology and data analysis plan. The chapter ends with information on threats to validity and ethical procedures.

Research Design and Rationale

Intervention

This study evaluated a mHealth ART appointment reminder intervention that was implemented at a public sector ARV clinic (Ward 21) located in the Hillbrow Community Health Center (HCHC) in Johannesburg, South Africa. HCHC offers secondary level health services in the inner city of Johannesburg, including maternal child health, TB, HIV, family planning, sexually transmitted illnesses management, plus minor surgeries and labor and delivery services. HCHC is also a referral center for public sector primary health care centers in the area and serves as a step-down facility for a tertiary level teaching hospital in Johannesburg. Ward 21 is an outpatient clinic and it is one of the largest clinics in Sub-Saharan Africa that provides free ART services.

The ART appointment reminder intervention was one of three mHealth intervention projects developed in response to pre- and post- ART patient attrition issues discussed in Chapter

2. All three interventions were pilot tested and revised based on the findings before being scaled up to the HCHC and two other primary health care (PHC) facilities in the HCHC's network.

One of the interventions was focused on provision of CD4 count by cell phone to ART naïve patients. This intervention was rolled out at the two PHCs only, since in South Africa, the outpatient HIV diagnosis and initial CD4 assessment primarily takes place at the PHC level. The other mHealth intervention pertained to ART adherence reminders. This intervention was originally planned to be offered to patients who had been on ART for more than 6 months. The mHealth team altered the project design at the time of roll out, and offered the adherence reminders to all patients on ART at the implementation sites. As part of this intervention, the participants received weekly adherence messages for 1 year. These messages had been field tested by one of the partnering mHealth organizations and included social, cultural, behavioral, nutritional and other messages to improve ART adherence. The CD4 by cell phone and ART adherence interventions mentioned above will be evaluated by other individuals and thus are not the focus of this study. The outcomes of the various evaluations, including this study, will be used to provide a comprehensive evidence base on the effectiveness of mHealth interventions in responding to the three key areas of concern affecting the HIV/AIDS care and treatment program in Sub-Saharan Africa and other countries.

The ART appointment reminder intervention was implemented at Ward 21 in September 2012, following positive outcomes from a pilot study conducted at one of the primary health clinics in this clinic's network. The intervention was originally planned for individuals newly initiating ART (less than 30 days). However, based on the pilot results, the project design was altered to offer and enroll everyone regardless of how long they had been on ART, to both the appointment and adherence reminder interventions. The content of the SMS messages for the

two interventions were distinct. Once enrolled in the ART appointment reminder intervention, the participants received an introductory e-mail, which was followed by three e-mail messages reminding the individuals of their scheduled appointments. These emails were sent 2 weeks prior to the appointment, 1 day prior to the appointment, and 1 day after the appointment. The pre-appointment messages were simple reminders that the client had an appointment on the particular date. The message after the appointment date varied based on whether the individual kept the clinic appointment or not. If the individual attended the clinic appointment, they received a message that thanked them for adhering to their appointment and reminded them of the next appointment date. If the individual missed their appointment then they received a message that informed them of the missed appointment and urged them to schedule another appointment. Figure 3 shows the messages sent to the participants.

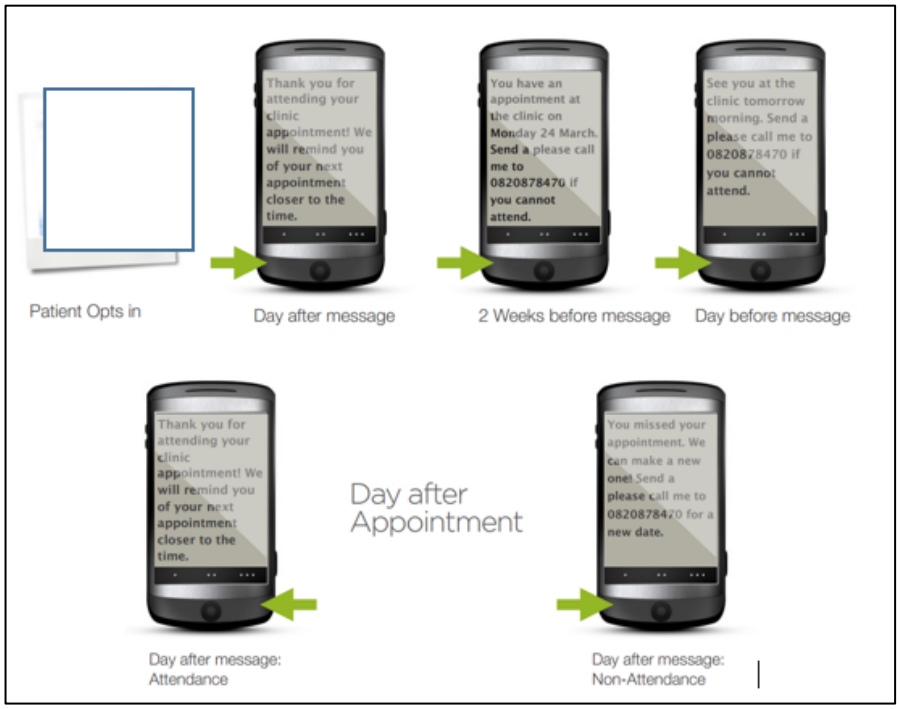

Figure 3. Appointment reminder intervention messages sent to the participants.

Research Design and Rationale

A large proportion of the existing primary research and knowledge base in the HIV/AIDS and mHealth field are pilot projects; there are few qualitative studies and even fewer clinical trials. There is an identified gap in the literature on studies conducted to evaluate the effectiveness of mHealth interventions in an HIV treatment setting, and specifically related to LTF. This study assisted in reducing the gap in the literature. The evaluation was based on a retrospective cohort study design to answer the question:

> Is there a difference in 6 and 12 month LTF rates between clients in the ART appointment reminder intervention and clients in the standard of care comparison group who did not receive the intervention, at Ward 21 in HCHC in Johannesburg, South Africa after controlling for the identified covariates?

The retrospective cohort nature of this evaluation, which used a baseline plus specific follow up period was consistent with the research design required to advance knowledge in the field of HIV/AIDS treatment. Six and twelve month LTF outcomes were ascertained among patients on ART at the clinic who had self-selected to enroll in the appointment reminder intervention between September 2012 and February 2013, and for a representative comparison group, which did not receive the intervention. This group only received the standard of care.

HIV treatment programs in South Africa and other countries are at highest risk of losing patients to LTF in the first 6 months of ART initiation (Dalal et al., 2007; Jaffer et al., 2007; Rosen & Ketlhapile, 2010; Yu et al., 2007,). The historical LTF statistics from this clinic indicated that this is not the case at Ward 21. Unpublished results from a 2008 patient file audit of over 6000 client files of clients who had initiated ART between April 2004 and March 2008 indicated a different LTF pattern at this clinic, as shown in Figure 4. The reasons for the

difference in LTF rates compared to other sites are unknown. The mHealth team took this information into consideration when implementing the appointment reminder intervention, and therefore decided to keep the recruitment criteria open to include patients who were either newly initiating ART (< 30 days) or who had been on ART for several months or years.

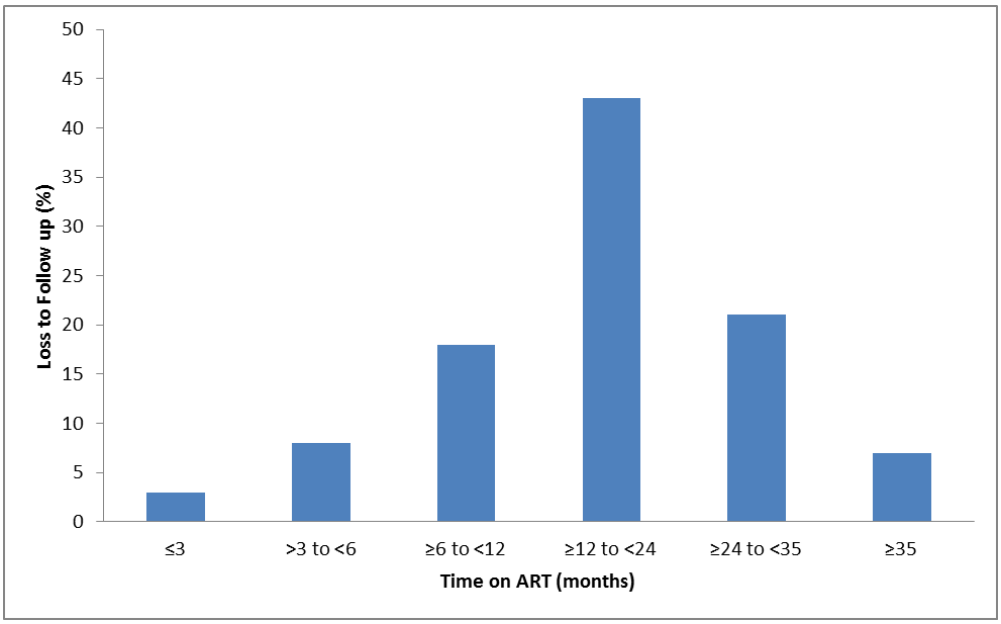

Figure 4. Distribution of patients lost to follow up at Ward 21, HCHC for period April 2004 to March 2008.

Major time and resource constraints were not expected since the study design required a retrospective review. Data collected by the program staff for project monitoring purposes, existing patient level data available at the clinic and if needed, the pharmacy databases were used as sources of information, therefore resource constraints were minimal. However, one of the disadvantages of using existing program data was that there was no guarantee that appropriate quality assurance measures were implemented during data collection and reporting. The actual time required to clean the data set in preparation for analyses was determined after the data was made available to the researcher.

Presence or absence of the appointment reminder intervention was the independent variable of this study. The dependent variables were LTF at six and twelve months after enrollment in the appointment reminder intervention during the specified study period of September 1, 2012 to February 28, 2013, and from September 1, 2012 for the comparison group.

Methodology

Population

The population for this study were the over 16,000 patients, 18 years and above, who had initiated on ART at either Ward 21 or at another facility and transferred to Ward 21, and were accessing follow up ART services at the clinic at the time of the implementation of the appointment reminder intervention. ART has been available to persons in the clinic's catchment area since 2004, and the population accessing services at this clinic is quite heterogeneous in that individuals from various ethnic, socioeconomic and cultural backgrounds reside in the clinic catchment area.

Sampling and Sampling Procedures

The intervention sample for this study comprised of all individuals eighteen years and older on ART at Ward 21 who enrolled in the intervention between September 1, 2012 and February 28, 2013 ($N = 806$). Information from figure 2, was used to categorize the study participants into six cohorts based on their duration on ART. The six cohorts and the estimated number of people in each of the intervention cohort according to the mHealth team were as follows:

Cohort 1 ($n = 91$). Initiated on ART between September 1, 2012 and February 28, 2013.

Cohort 2: ($n = 123$). Initiated on ART between 1-6 months prior to Sept 1, 2012.

Cohort 3: ($n = 86$). Initiated on ART between 7-12 months prior to Sept 1, 2012

Cohort 4: (n = 193). Initiated on ART between 13-24 months prior to Sept 1, 2012

Cohort 5: (n = 150). Initiated on ART between 25-36 months prior to Sept 1, 2012

Cohort 6: (n = 163). Initiated on ART >36 months prior to Sept 1, 2012

The comparison sample for this study was identified using partly purposeful, partly random stratified approach where by the demographic profile of the intervention group (age and gender), and time on ART was used to create matching criteria to align the comparison and the intervention groups. Comparison group comprised of individuals who were on ART and received the standard of care at the clinic but who did not receive the intervention. The researcher expected a higher chance of missing or incorrect information in the comparison group as the clinic's data quality practices were not clear. Therefore, the sample size of the comparison groups was estimated approximately 20% higher than the sample size of the intervention group. Consequently, the number of individuals in each of the comparison group cohorts were oversampled to accommodate for missing or incorrect information.

SPSS version 21was used to randomly select the individuals for the six comparison cohorts. Drawing the study samples from the same clinic population assisted in reducing variations and confounding, although there was a possibility of selection bias as the individuals had self-selected to enroll in the intervention. The inclusion criteria for the study was all adult (18 years and above) male and female (including pregnant) patients. The only exclusion criteria was patients under 18 years of age.

A power analysis via G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) was conducted to determine the necessary sample size required per cohort group for a logistic regression analysis, which was used to address the study research questions. For the power analysis, specific input parameters were entered which were: effect size, set at medium, $f^2 = .30$, power set

at .80, and the significance (p) set at < 0.05. Based on these parameters, the total sample size per group required to achieve adequate statistical power was $N = 176$. The actual sample sizes for the intervention and comparison groups exceeded this value.

Procedures for Recruitment, Participation, and Data Collection

The mHealth team at the host institution, Wits Reproductive Health and HIV Institute (WRHI), in Johannesburg obtained IRB approval from the Witwatersrand (Wits) University to implement the mHealth interventions and conduct formative, evaluative and other research activities in relation to these projects. As part of the Wits University IRB requirement, the team was required to acquire approval from the Provincial Department of Health to conduct the mHealth projects at the DoH ART clinics and to access the clinic and pharmacy patient records for the intervention and subsequent evaluations. Copies of the Wits IRB and DoH approval letters were included as supporting documents in the Walden IRB package. Individuals enrolled in the post-ART interventions had the option to opt out at any time. Patients opting out received a follow up call from the project staff to confirm the decision, and to ascertain the reason for opting out.

The mHealth team recruited fieldworkers and placed them at Ward 21 after a rigorous training and mentoring phase, which emphasized on patient recruitment methods, patient confidentiality, data quality, quality assurance, and other items. The field workers were present at the clinic every day. They approached patients in the waiting room, ascertained if the patient were on ART, explained the intervention, and asked the patients if they wanted to enroll. If the patients agreed to participate in the intervention, the fieldworkers walked them through an informed consent process. The consent form was approved by the Wits University IRB. It included items such as participants giving permission to receive SMS appointment reminders, be

contacted by phone (if needed for follow-up), and for use of their clinical information for program improvement, research and evaluation activities.

The mHealth team had developed data capturing tools that included patient intake and follow up forms and an electronic database. The field workers collected the information in the intake forms and transferred it to the database each day. An electronic patient management and a pharmacy dispensing system is used at the clinic, and the program team accessed this system to obtain patients' demographic, clinical, and follow-up appointment information. The mHealth team used patients' clinic ID numbers as identifiers in the project database. As per Wits IRB requirements, the patient level information was accessed only by key project personnel and was stored appropriately to maintain patient confidentiality.

Approval was obtained from WRHI to request retrospective program data from September 2012 to June 2014. This covered the twelve month plus 90 days follow-up period for all the individuals who enrolled in the intervention between September 2012 and February 2013. Figure 5 provides information on the timelines to ascertain LTF status at six and twelve months after enrollment in the intervention. Determination of LTF at 90 days after the end of six and twelve months of enrollment was based on the PEPFAR definition of assigning the LTF status (PEPFAR SASI Manual, 2007). In addition, permission was obtained to receive data from the clinical and the pharmacy databases for demographic, clinical, and appointment information for the intervention and comparison groups. For the comparison group, the six and twelve months LTF status were determined from September 1, 2012.

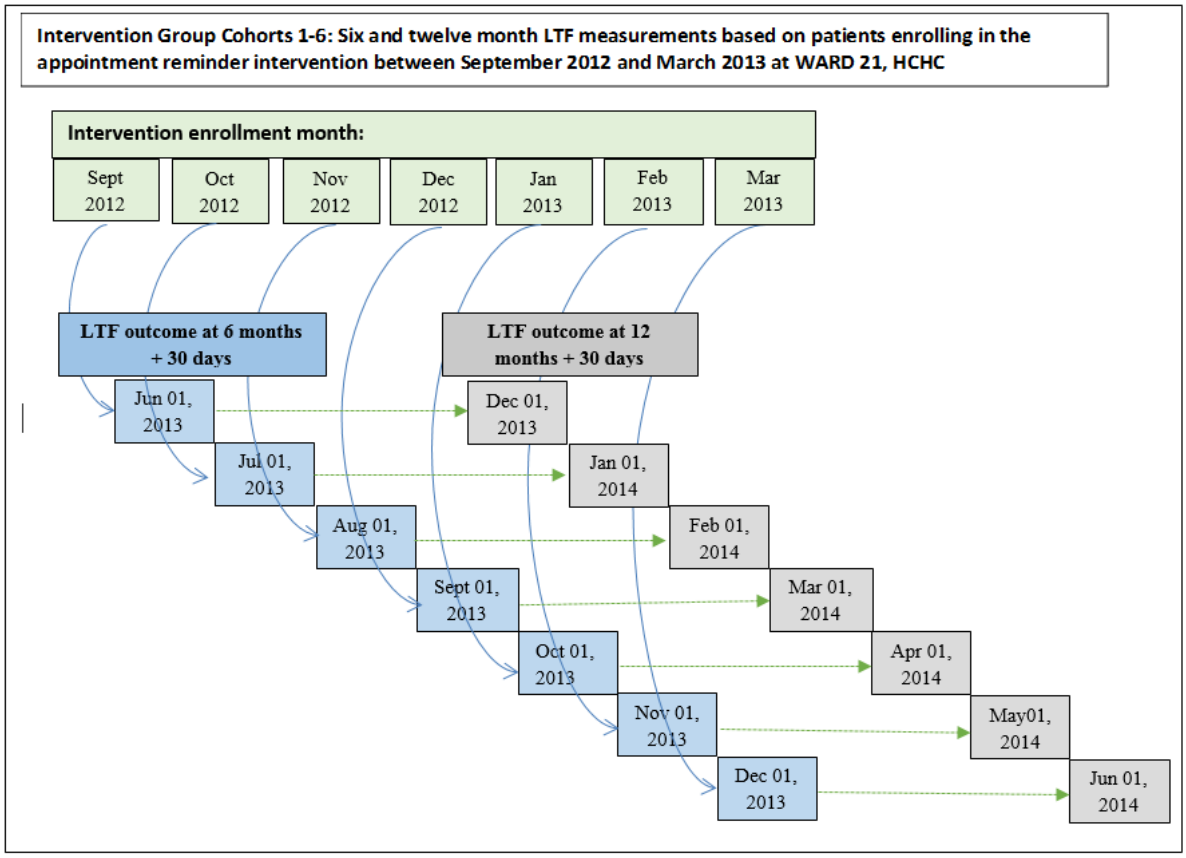

Figure 5. Data analysis timeline to ascertain loss to follow up in the study cohorts, six and twelve months after enrolling in the intervention.

Instrumentation and Operationalization of Constructs

Operationalization of Variables

Independent Variable. The key independent variable for this study was the presence or absence of the ART appointment reminder intervention. This independent variable was dichotomously coded where 0 = standard of care and 1 = ART appointment reminder intervention. Clients should have received all three of the reminders per appointment period to be included in the intervention group.

Covariates. Covariates are variables, which may not be part of the main study inquiry however, they can influence the dependent variable (Field, 2012). The covariates for this study were identified based on information found in the literature from studies on mHealth and

adherence to ART (Lester et al, 2010; Pop-Eleches, 2011; Rodrigues et al, 2012). The study covariates and their operational definitions are presented below:

Age. Client age at initiation of ART was used as a measure of age. Age is a ratio variable and will be calculated in years.

Gender. Gender is a dichotomous variable where 1 = male and 0 = female.

Baseline CD4 count. CD4 count is the number of CD 4 cells, a type of white cell that fights infection. A low baseline CD4 count can put a person at a high risk of getting sick. It can have an effect on adherence to ART appointment and loss to follow up. A CD4 count is a ratio variable, as it can range from 0 cells/mm^3 to 1,500 cell/mm^3. A normal CD4 count ranges between 500 to 1,500 cells/mm.[3] In South Africa, ART is recommended when the CD4 count is below 350 cells cell/mm^3 (Carter and Hughson, 2014; South African ART Guidelines, 2013). The baseline CD4 count is the count taken three months before ART initiation.

ART regimen. This covariate is a categorical variable based on four different types of ART regimens, and it is coded where 1 = Regimen 1A, 2 = Regimen 1B, 3 = Regimen 2, and 4 = Other Regimen.

Concurrent illnesses. This covariate was based on the presence of concurrent illnesses as noted in the patient's records. This variable was dichotomously coded where 0 = no concurrent illnesses and 1 = yes, concurrent illnesses.

ART side effects. This covariate is based on evidence of ART side effects as noted in the patient's records. This variable was dichotomously coded where 0 = no ART side effects and 1 = yes, presence of ART side effects.

Dependent Variables: LTF. There were two dependent variables in this study, both of which pertained to LTF. Programmatically, LTF is defined as the disappearance of the

individuals from ART for no known reason (Rosen et al., 2007). For the purpose of this study a patient was considered LTF if they have not been to the clinic or picked up their ARVs for at least 3 consecutive months. (PEPFAR Strategic Information Manual South Africa, 2007). Data on individuals who had died during the study period were noted but not included in the analysis. There were two LTF dependent dichotomously coded variables: (a) 0 = no, no loss of client at follow up at 6 months and 1 = yes, loss of client at follow up at 6 months and (b) 0 = no, no loss of client at follow up at 12 months and 1 = yes, loss of client at follow up at 12 months. The two time periods were selected based on evidence from mHealth based ART adherence studies found in the literature. These studies found significant differences in adherence to ART at the six and twelve month timeframes (Lester et al, 2010; Rodrigues et al, 2012).

The study data was planned to be derived from four sources: (a) ART appointment reminder intervention data from the project database; (b) patient demographic and clinical data from the Electronic Medical Records (EMR), of patients who initiated on ART between September 2012 and February 2013 and for the relevant comparison groups by cohort; (c) patient appointment dates from the EMR or electronic pharmacy dispensing system for patients who initiated on ART between September 2012 and February 2013 and for the relevant comparison groups by cohort; and (d) the 2009 HCHC File Audit Report (unpublished).

Data Analysis Plan

The purpose of this study was to evaluate the effectiveness of a mHealth patient appointment reminder intervention to improve retention in care of patients initiating ART at a large public sector ART clinic in Johannesburg, South Africa.

Research question 1. Is there a difference in six month LTF rates between clients in the ART appointment reminder intervention and clients in the standard of care comparison group

who did not receive the intervention, at Ward 21 in HCHC in Johannesburg, South Africa after controlling for the identified covariates?

$H_{o1.}$ There are no statistically significant decreases in the likelihood of 6 month LTF for clients on ART who received the appointment reminder intervention when compared to clients in the standard of care comparison group.

$H_{a1.}$ There are statistically significant decreases in the likelihood of 6 month LTF for clients on ART who received the appointment reminder intervention when compared to clients in the standard of care comparison group.

Research question 2. Is there a difference in 12-month LTF rates between clients in the ART appointment reminder intervention and clients in the standard of care comparison group who did not receive the intervention, at Ward 21 in HCHC in Johannesburg, South Africa after controlling for the identified covariates?

$H_{o2.}$ There are no statistically significant decreases in the likelihood of 12 month LTF for clients on ART who received the appointment reminder intervention when compared to clients in the standard of care comparison group.

$H_{a2.}$ There are statistically significant decreases in the likelihood of 12 month LTF for clients on ART who received the appointment reminder intervention when compared to clients in the standard of care comparison group.

The project data was obtained in Microsoft Excel file formats from the mHealth project staff. Additional demographic and study related data was be included in this database as relevant. All study data was cleaned (i.e., reviewed for errors) then exported to a SPSS 21.0 data file for data analysis. All of the study variables were assigned a variable name, with the variable values coded (e.g., male = 1 and female = 0). Cases were reviewed for missing at random (MAR) and

not missing at random (NMAR) data, and multiple analyses were conducted on the NMAR data (Agresti, 2013). Descriptive statistics were computed for the study variables, inclusive of the study covariates. The mean, standard deviation, and minimum and maximum values were computed for ratio variables and frequencies and percentages calculated for dichotomous and categorical variables. Outliers were addressed by replacing the outlier with the next highest or lowest value (Agresti, 2013). Spearman's rho correlations and chi-square analyses were conducted between each of the identified study covariates and the dependent LTF variables. Covariates found to be associated with the dependent variables with p-values of < 0.25 were included as predictors in the logistic regression analyses performed to address the study research question. The p-value criteria of < 0.25 for covariate association was used for analysis as it is possible that a covariate may not be significantly associated independently but may contribute to the model in conjunction with other variables.

A benefit of using logistic regression is that the assumptions of normality, linearity, and homogeneity of variance are not relevant to this type of statistic as thus data need not be examined for violations of these assumptions (Agresti, 2013). Two binary logistic regression analyses were conducted for the two dependent variables (LTF at 6 months and LTF at 12 months). Binary logistic regression was selected for this study as the dependent variables were dichotomously coded and the relationship between the intervention and the outcomes of LTF could be determined when covariate variance were accounted for (Agresti, 2013). The model chi-square (χ^2) determined the significance of the overall regression model, while the classification table generated by the statistical tool determined correct classification of the dependent variable categories based on the predictors in the model (Agresti, 2013). The Hosmer-Lemeshow (H-L) statistic for logistic regression, which answers the question, "how best does my

model fit the data?" was used as the model goodness-of-fit statistic (Allison 2013). If the *p*-value produced from the statistic was low (< .05) then the model was rejected. If the *p*-value was high, then the model passed the test as a good fit (Allison 2013; Agresti, 2013). Any probability value of significance (*p*-value) generated in the regression model, which was less than the level of significance (0.05) was considered statistically significant.

Threats to Validity

It is important to note the potential threats that can affect the validity of the study. The most common threats are to the internal, external and statistical conclusion validity. Threats to internal validity compromise the researcher's confidence to indicate if a relationship exists between the independent and dependent variables. Information presented below was developed based on the list of threats to internal validity by Michael (2014). History should not be a threat to this study as both the intervention and control groups were from the same clinic and had initiated on ART during a similar time period. If an unexpected event occurred during the study period, which may affect the outcome noted, it would have affected both the groups and thus should not have an effect on the differences noted between the two groups. Maturation was not a threat to this study as both the groups experienced the same progression of their illness at the same rate. Selection bias was a possible threat to the internal validity of this study as the participants self-selected to enroll in the intervention. Experimental mortality or the attrition in number of participants over the study period could have been a minor threat to this study, however, the full extent of this threat could only be ascertained once data was received for analyses. That said, the mHealth project manager has mentioned to the researcher that individuals asking to opt out of the intervention were few. The project collected information on the reason for opting out which was reviewed as part of this study. Testing was not part of this

intervention therefore it was not a valid threat. The dependent variables were measured using the project and clinic data for both the groups, thus instrumentation was not a threat for this study. Design contamination could have been a possible threat to this study, especially since all individuals were approached and the intervention was explained and offered to everyone. In addition, all individuals enrolled in the appointment reminder intervention also received weekly adherence messages. It was difficult to confidently state if the outcomes observed were a result of the appointment reminder or the adherence messages. It was not possible to control for the adherence intervention as the study used retrospective data. It would have been a better practice if the groups of individuals who received the two interventions (appointment reminder and adherence messages) were kept separate as originally planned. Full extent of this issue may become apparent at the time of data analysis. Compensatory rivalry and resentful demoralization did not affect this study as the intervention was offered to all the patients on ART (Michael, 2014).

According to Michael (2014), threats to external validity can compromise confidence in making the study results generalizable to other populations. Some important threats to external validity are: i) interaction of testing, ii) interaction effects of selection biases and the experimental treatment testing reactivity, iii) reactive effects of experimental arrangements, and iv) multiple-treatment interference.

Interaction effect of testing occurs when a pre-test interacts with the intervention under study and alters the outcomes such that the results cannot be generalizable beyond the study population (Michael, 2014). This phenomenon was not a threat to this study as the participants were not tested during the course of the intervention. Interaction effects of selection biases and the experimental treatment takes place when some aspect of the group based on the selection of

the participants interacts with the intervention, which would not have happened if the participants were randomly selected (Michael, 2014). This was a potential threat to this study as the participants self-selected to receive the intervention. Reactive effects of experimental arrangement also known as the Hawthorne effect is a phenomenon experienced by some participants who may alter their behaviors because they are part of a study (Michael, 2014). This could have been a viable threat to this study. It is possible that the participants receiving the intervention altered their treatment adherence. Multiple treatment interference occurs when subjects are given multiple doses of the treatment or, as is the case in a repeated measures study design. This makes it difficult for the researcher to generalize the results to the actual effect of a single treatment (Michael, 2014). While this study population will be measured repeatedly for adherence to appointments and LTF, multiple treatment interference was not a viable threat to this study population based on the planned intervention, which sent a set number of reminders to the participants every month.

Threat to construct or statistical conclusion validity (SCV) comes into play when inappropriate or inadequate statistical analysis are used for data analysis or measurement of variables, which produce results that would have been different if the correct data analysis tool were utilized (Garcia-Perez, 2012). A threat to SCV can lead the researcher to incorrect conclusions about the relationship between the indirect and direct variables. They can lead to two main types of errors: (a) the researcher concludes that there is no relationship when in reality there is a relationship or (b) the researcher concludes that there is a relationship when in reality there is no relationship. These are similar to the Type I and Type II errors that can be encountered in hypothesis testing. Some of the common threats to SCV according to a WEB center for social research methods article (2014) include: (a) slow reliability of measures, (b)

poor reliability of treatment implementation, (c) random heterogeneity of respondents, (d) low statistical power, and (e) violated assumptions of statistical tests.

Low reliability of measures comes up if the measurement tool is not appropriate. That is, there is poor layout or design of the tool or questions that may not be appropriate for the study. Poor reliability of treatment implementation is particularly important in an evaluation setting. This occurs, when the program is not implemented as planned or there are inconsistencies in the actual implementation. This can make it difficult to ascertain relationships between the independent and dependent variables. Random heterogeneity of the respondents pertains to the different types of people who may be participating in the study, which would increase variance in the responses. Some of the variability may be useful for the study while others could potentially cause hindrance in observing any relationships. The above three items may mask actual relationship; however, the strongest threat to SCV is low statistical power. This affects the strength of any relationship or associations. Violated assumptions of statistical tests are important as a researcher can make incorrect assumptions when conducting data analysis; for example, assuming that the data is normally distributed when it is not (WEB center for social research center, 2014).

Some of the recommendations based on the above mentioned threats to SCV include: using robust statistical power, ensuring appropriate reliability, implementation of the intervention, and good understanding about the data and use of appropriate statistical tests. The sample size for the intervention group was pre-determined for this study and individuals on ART at the clinic who had not received the intervention were randomly sampled for inclusion in the comparison group. The total sample size was large enough to provide a strong power for this study. The intervention did not use any tools to measure study variables, it used actual data from

the clinic and pharmacy. Therefore, the study was not at risk for inappropriate reliability. Appropriate implementation of the intervention could be an area of concern for this study. The WEB center for social research center (2014), has recommended that to achieve good implementation of intervention researcher should have standardized protocols and train the program staff to implement the intervention uniformly and appropriately. The mHealth team had trained and mentored the field workers and other program staff on appropriate participant recruitment, patient confidentiality, follow up, and data quality, so the effect of this threat were minimal to this study. In addition, the team had developed Standard Operating Procedures and recruitment flow charts for the fieldworkers to use in their day-to-day project tasks. To avoid violated assumption of statistical tests, the researcher shared the analysis plan with the dissertation committee before starting the analysis.

Ethical Procedures

As mentioned earlier, the project team had submitted an application to the Wits University IRB to implement the three mHealth interventions and evaluate them. As part of the Wits IRB application, the project had to obtain a letter of approval from the provincial DoH leadership to implement the project at the DoH sites in the inner city of Johannesburg. The Wits IRB application was approved in 2012, and the approval letter was included in the Walden University IRB application. Letters of permission to access the project and clinic data were obtained for this study from WRHI and included in the IRB application and/or the final dissertation as required.

Ethical concerns in relation to recruitment materials and processes, data collection, and intervention activities were not expected given the retrospective nature of this study, and since no new data was collected as part of this evaluation study. The appointment reminder project was

described as a low risk intervention by the WRHI mHealth team in the Wits University IRB application, which means that the participants had low risk of adverse events resulting from participating in the project. The mHealth team used specific measures to protect patient confidentiality in line with the Wits University IRB requirements. As mentioned earlier, the project used patient clinic IDs to link with the clinical information and for follow up activities, in an effort to protect participant confidentiality. Once the Walden IRB approval was received (IRB approval number 10-15-14-0108616), the WRHI mHealth team made the project data available to the researcher. In addition, specific demographic and clinical information on the patients in both the intervention and comparison group from the clinic's EMR and pharmacy databases was requested by the researcher. Walden IRB required the researcher to not have access to the patient's clinic ID numbers. The researcher was the only person to have access to the raw data for the study. The study database was password protected and stored on the researcher's personal computer at home. The study database will be deleted from the computer five years after the completion of the dissertation or as required by the Walden University IRB.

This study was conducted at the researcher's previous place of employment. As the head of department for the Monitoring and Evaluation (M&E) team at WRHI from 2006 - 2013, the researcher supervised five portfolios in the department. However, all the portfolios were managed by program managers. While the researcher provided technical assistance to the mHealth portfolio and supervised the program managers, the mHealth program manager had recruited the mHealth team members and managed the day-to-day functioning of the portfolio. The researcher was not involved with the training of the intervention staff and did not have access to the project data prior to the evaluation, except for the routine program monitoring outputs reported by the team via quarterly reports. The researcher left WRHI to relocate to the

US in March 2013 and has not had any management or technical connections to the M&E team since.

WRHI leadership promotes and supports its staff to pursue higher educational degrees. Four M&E staff members are pursuing or completed their Masters degrees in the last five years. One of the program managers already has a PhD and three of the remaining four are currently pursuing their PhDs – two of the dissertation topics are mHealth related, therefore there is no risk of power differential regarding this dissertation. Furthermore, based on the independent mHealth dissertations underway, the two program managers and the researchers expect to provide a well-rounded evidence base on the effectiveness of mHealth in strengthening HIV/AIDS care and treatment in South Africa.

Summary

This evaluation was based on a retrospective cohort study design using quantitative analysis. The effectiveness of appointment reminders sent via SMS, in reducing missed appointments among individuals enrolled in the intervention versus individuals not enrolled in the intervention was ascertained by this study. Loss to follow up rates at six and twelve months post ART initiation were also reviewed for the above two groups. The appointment reminder intervention is one of first mHealth projects to be implemented in South Africa and the results from the evaluation are expected to have an effect on the expansion of other mHealth and HIV projects in South Africa.

While this chapter provided information on the study methodology and data analysis plan, the next chapter includes actual data from the study, analysis of the data, study observations and explains any deviations or alterations to the information in this chapter.

Chapter 4: Results

Introduction

The purpose of this study was to evaluate the effectiveness of a mHealth patient appointment reminder intervention to improve retention in care of patients initiating ART at a large public sector ART clinic located in a community health center in Johannesburg, South Africa. The two research questions queried differences in LTF rates at 6 and 12 – months between clients enrolled in the ART appointment reminder intervention and clients in the comparison group. The hypotheses were that there were no statistically significant differences in the LTF rates at 6 and 12 months, between the intervention and the comparison groups.

This chapter starts with information on the research questions, and the null and alternate hypotheses. This is followed by tables with descriptive statistics on the basic demographics and various study covariates of the two study groups. Chi-square and regression analyses between the covariates and the dependent variables form the next part of this chapter. A model chi-square analysis for the full study population is presented first, followed by cohort-level chi-square and regression analyses for each of the six cohorts in the study. The chapter ends with a summary of the findings and introduction to Chapter 5.

Data Collection

As mentioned in Chapter 3, the project data requested from the host organization was for the period September, 2012 to June, 2014. However, the organization was able to provide data for this period only for the intervention group. Data for the comparison groups was available through January 2014. In 2011, the national DoH made a decision to roll out a standardized HMIS called Tier.net at all the public sector HIV clinics in the country. The accompanying new policy mandated all sites to shut down any existing HMIS and switch to the new DoH one. Ward

21, the study site, was allowed a 2-year grace period to shift to the new system as the existing HMIS in use at the clinic was more advanced than Tier.net. In December 2013, the DoH asked the site to switch over to Tier.net immediately, thus the time period for the data for the comparison group was shortened to January, 2014. Nonetheless, the truncated period did not impact this study and it was possible to make LTF decisions at the 12-month mark for all the patients in the intervention and the comparison groups. The researcher also noted that individuals who were identified as LTF at 6 months continued to be LTF at 12 months.

According to the preliminary information from the intervention implementation team, 806 individuals were expected to be in the intervention group. As mentioned in chapter three, the comparison group cohorts were to be oversampled by approximately 20%. In actual, a total of 832 individuals qualified to be included in the intervention group during the study enrollment period of September 1, 2012 to February 28, 2013. The actual size of the comparison group was 918, for a total study population of 1750 individuals. Participants were randomly selected for the comparison group based on the gender and age breakdown of the six intervention group cohorts. Data cleaning was conducted before the analyses; any individuals who did not have an ART initiation date or were LTF before September 2012 were removed from the dataset.

The study sample size was $N = 1750$ participants (832 in the intervention group and 918 in the comparison group), of whom $n = 1135$ (64.9%) were female and $n = 615$ (35.1%) were male. The demographic and descriptive characteristics of the sample population are summarized in Table 1. The mean age of participants was 37.34 years ($Md = 36.00$, $SD = 8.25$), and participants ranged in age from 18 to 79 years. Of the $n = 832$ participants in the intervention group, $n = 523$ (62.9%) were female and $n = 309$ (37.1%) were male. The mean age of intervention group participants was 37.41 years ($Md = 36.50$, $SD = 8.11$), and intervention

participants ranged in age from 18 to 67 years. Of the *n* = 918 participants in the comparison group, *n* = 612 (66.7%) were female and *n* = 306 (33.3%) were male. The mean age of the comparison group participants was 37.28 years (*Md* = 36.00, *SD* = 8.38), and the participants in this group ranged in age from 19 to 79 years. Of the 1135 females in the study group, *n* = 61 (5.4%) were pregnant. Of these, *n* = 27 were in the intervention group and *n* = 34 were in the comparison group.

Table 1
Study Participants by Group (N = 1750)

	Intervention *n* = 832		Comparison *n* = 918	
	Frequency	Percentage	Frequency	Percentage
Gender				
Female	523	62.9	612	66.7
Male	309	37.1	306	33.3
Cohort				
1	88	10.6	107	11.7
2	102	12.3	136	14.8
3	77	9.3	84	9.15
4	184	22.1	196	21.3
5	190	22.8	204	22.2
6	191	22.9	191	20.8
Pregnant				
No	496	94.6	578	94.1
Yes	27	5.4	34	5.9
	Mean	SD	Mean	SD
Age	37.41	8.11	37.28	8.38

A chi-square (χ^2) test of independence showed that there was a slight but significant association between gender and the intervention and comparison group classification, $\chi^2 = 2.77$,

p = .01. An independent samples t-test showed that the intervention and comparison groups of participants did not significantly differ on age, t (1748) = 0.34, p = .73. Table 2, shows breakdown for gender by the intervention and comparison group cohorts and table 3, provides the age breakdown information by each cohort in the two study groups.

Table 2
Study Participants Gender by Intervention and Comparison Group Cohorts (N = 1750)

		Intervention (*n*=832)		Comparison (*n*=918)	
		Frequency	Percentage	Frequency	Percentage
Cohort 1	Female	55	62.5	72	67.3
	Male	33	37.5	35	32.7
Cohort 2	Female	60	58.8	89	65.4
	Male	42	41.2	47	34.6
Cohort 3	Female	43	55.8	58	69.0
	Male	34	44.2	26	31.0
Cohort 4	Female	120	65.2	128	65.3
	Male	64	34.8	68	34.7
Cohort 5	Female	123	64.7	132	64.7
	Male	67	35.3	72	35.3
Cohort 6	Female	122	63.9	133	69.6
	Male	69	36.1	58	30.4

Table 3
Study Participant Mean Age by Intervention and Comparison Cohorts (N = 1750)

	Intervention (*n* = 832)		Comparison (*n* = 918)	
	Mean Age (years)	*SD*	*Mean Age (years)*	*SD*
Cohort 1	35.25	8.17	36.29	9.44
Cohort 2	36.28	8.64	36.03	8.09
Cohort 3	37.21	8.50	37.74	9.08
Cohort 4	36.39	7.43	36.14	8.29
Cohort 5	37.24	7.98	37.75	7.64
Cohort 6	40.25	7.75	39.18	8.17

Results

Descriptive Statistics: Study Population

Analyses were done to ascertain the first, baseline and most current CD4 counts of the individuals in the study groups. First CD4 counts were found for *n* = 1519 (87%) of the study population. Baseline CD4 counts were available for *n* = 1395 (80%) of the study population. It was noted that of the *n* = 355 (20%) of individuals with missing baseline CD counts, approximately *n* = 162 (50%) had transferred into this clinic after initiating ART at another clinic. If the individuals' record was missing a baseline CD4 count, but had a first CD4 count, then the difference between the date of the first CD4 count and ART initiation date was ascertained. If the first CD4 count date was less than six months prior to the ART initiation date, then the first CD4 count value was used as the baseline CD4. The median first CD4 count for the entire study population was 148 cells/mm^3 while the median baseline CD4 count for the entire

study population was 137 cells/mm^3. Current CD4 counts were available for *n* = 1708 (98%) of the study population. The median current CD4 count for the entire study population was 384 cells/mm^3. Median baseline and current CD4 counts by intervention and comparison group cohorts are presented in table 4. In cases where a value was missing for variables first reported CD4 or baseline CD4 or current CD4, a mean value substitution was done. The median figures presented above for first, baseline and current CD4 count data were before the mean value substitutions were done.

Table 4
Baseline and Current CD4 Median by Intervention and Comparison Group Cohorts (N = 1750)

	Intervention *(n* = 832*)*		Comparison *(n* = 918*)*	
	Baseline CD4 (cells/mm^3)	Current CD4 (cells/mm^3)	Baseline CD4 (cells/mm^3)	Current CD4 (cells/mm^3)
All cohorts	137	391	137	379
Cohort 1	157	299	188	271
Cohort 2	202	350	181	311
Cohort 3	165	325	157	323
Cohort 4	130	385	136	366
Cohort 5	124	403	106	425
Cohort 6	111	485	120	514

Note: The median CD4 values in table 4 are based on data before mean value substitutions were done for missing CD4 data. For the rest of the analyses for this study, the mean value adjusted first, baseline and current CD4 values have been used.

Current viral load was one of the study covariates. This information was available for 95% (*n* = 1672) of the study population. Viral load is one of the markers used to detect ART success or the ability of the ART to keep the virus level under control. Viral load is measured in terms of virus copies per milliliter of blood. Viral load of < 49 virus copies/ml of blood is considered undetectable (http://www.aidmap.com). A viral load of > 49 virus copies /ml of

blood should be a red flag for health care providers to query possible ART adherence issues or possible ART failure. A viral load of < 49 virus copies/ml of blood is referred to as undetectable while a viral load of > 49 virus copies/ml of blood is considered to be in the detectable range. Of the 1672 individual who had current viral load information available, *n* = 1455 (87%) had an undetectable viral load. The virus was detectable in *n* = 126 (15%) and *n* = 91 (10%) of the individuals in the intervention and comparison groups respectively.

A large variation in the viral load range in individuals with detectable viral load values was found. Median substitutions were done in some cases as there were some major outliers, which were affecting the mean values. A median value was more representative of the values in the large sample, but even this led to values in the regressions that were not interpretable (*b* = 0.000). Transforming the median current viral load into a z-score led to more useful information, which was used for all the regression analyses.

For the purpose of this study, current ART regimen was defined as the ART regimen the patient was on between June 2012 (three months prior to the study period) and January 2014 (the study end period). The South African government released new guidelines for ART regimens in 2013 (The South African Antiretroviral Treatment Guidelines, 2013). According to the new guidelines, the regimens were re-categorized as regimen 1 and 2 versus the previous guidelines (included in chapter 3), which had the categorization of regimen 1A, 1B and 2. The updated 2013 guidelines were used during data analysis. ART regimen data was available for all 1760 individuals in the study. Most of the individuals were on the first line regimen *n* = 1465, (83.7%) during the study period. The remaining 285 (*n* = 16.3%) individuals were on the second line regimen. Changes in regimen during the study period were not noted during analysis. Table 5,

includes ART regimen information disaggregated by the six cohorts in both the intervention and the comparison groups.

Table 5
First and Second ART Regimen by Intervention and Comparison Goup Cohorts (N = 1750)

	Intervention Group *(n* = 832*)*				Comparison Group *(n* = 918*)*			
	First ART Regimen		Second ART Regimen		First ART Regimen		Second ART Regimen	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*
All cohorts	685	82.3	147	17.7	780	85.0	138	15.0
Cohort 1	86	97.7	2	2.3	101	94.4	6	5.6
Cohort 2	97	95.1	5	4.9	128	94.1	8	5.9
Cohort 3	66	85.7	11	14.3	80	95.3	4	4.8
Cohort 4	153	83.2	31	16.8	168	85.7	28	14.3
Cohort 5	144	75.8	46	24.2	165	80.9	39	19.1
Cohort 6	139	72.8	52	27.2	138	72.3	53	27.7

Table 6, provides descriptive statistics for individuals who transferred into the clinic after initiating ART at another clinic and for individuals who initiated on ART at the study clinic but transferred out to another clinic. Individuals transferred in and transferred out may not be the same. Individuals who had transferred out were considered retained on ART.

Table 6
Transfers In and Transfers Out by Intervention and Comparison Group Cohorts (N = 1750)

	Intervention Group (n = 832)				Comparison Group (n = 918)			
	Transferred in		Transferred out		Transferred in		Transferred out	
	n	%	*n*	%	*n*	%	*n*	%
All Cohorts	205	24.6	35	4.2	80	8.7	49	5.3
Cohort 1	2	2.3	5	5.7	4	3.7	3	2.8
Cohort 2	9	8.8	0	0.0	2	1.5	8	5.9
Cohort 3	10	13.0	1	1.3	3	3.6	5	6
Cohort 4	34	18.5	11	6.0	14	7.1	6	3.1
Cohort 5	48	25.3	11	5.8	9	4.4	8	3.9
Cohort 6	102	53.4	7	3.7	48	25.1	49	5.3

Descriptive statistics were ascertained for individuals who had ART side effects: lipodystrophy, lactic acidosis and/or peripheral or poly neuropathy listed in their records. These were the three most commonly noted side effects found during the 2009 patient file audit conducted at this clinic, thus these side effects were used in this study. Similarly, a few of the more commonly associated co-morbidities with HIV, namely tuberculosis, herpes zoster and kaposi sarcoma identified via a patient file audit conducted at this clinic in 2009 (unpublished report), were included in the analyses. Tables 7 and 8 include the descriptive statistics for the side effects and the co-morbidities found in the patients' clinical records. Three individuals had more than one side effect or co-morbidity concurrently reported during the study period.

Table 7
Lipodystrophy, Lactic Acidosis, and Peripheral/Poly Neuropathy Rates by Intervention and Comparison Group Cohorts (N = 1750)

	Intervention Group (*n* = 832)						Comparison Group (*n* = 918)					
	LIPO		LA		PNP		LIPO		LA		PNP	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
All cohorts	26	3.1	1	0.1	15	1.8	88	9.6	14	1.5	53	5.8
Cohort 1	0	0.0	0	0.0	1	1.1	0	0.0	0	0.0	1	0.9
Cohort 2	3	2.9	0	0.0	5	4.9	0	0.0	0	0.0	4	2.9
Cohort 3	1	1.3	0	0.0	1	1.3	0	0.0	0	0.0	0	0.0
Cohort 4	2	1.1	0	0.0	1	0.5	3	1.5	0	0.0	0	0.0
Cohort 5	7	3.7	0	0.0	5	2.6	28	13.7	7	3.4	16	7.8
Cohort 6	13	6.8	1	0.5	2	1.0	57	29.8	7	3.4	28	14.7

Note. LIPO = Lipodystrophy; LA = Lactic Acidosis; PNP = Peripheral/Poly Neuropathy.

Table 8
Tuberculosis, Herpes Zoster, and Kaposi Sarcoma Rates by Intervention and Comparison Group Cohorts (N = 1750)

	Intervention						Comparison					
	TB		HZ		KS		TB		HZ		KS	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
All cohorts	40	4.8	19	2.3	1	0.1	22	2.4	7	0.8	1	0.1
Cohort 1	11	12.5	6	6.8	0	0.0	12	11.2	3	2.8	1	0.9
Cohort 2	13	12.7	2	2.0	0	0.0	6	4.4	3	2.2	0	0.0
Cohort 3	4	5.2	3	3.9	1	1.3	0.0	0.0	0	0.0	0	0.0
Cohort 4	3	1.6	2	1.1	0	0.0	1	0.5	0	0.0	0	0.0
Cohort 5	5	2.6	3	1.6	0	0.0	2	1.0	0	0.0	0	0.0
Cohort 6	4	2.1	3	1.6	0	0.0	1	0.5	1	0.5	1	0.1

Note. TB = Tuberculosis; HZ = Herpes Zoster; KS = Kaposi Sarcoma.

Most of the individuals enrolled in the intervention were retained in the program at the time of this evaluation. Only *n* = 8 (1%) individuals in the intervention group opted out.

Testing of Covariates and Logistic Regression Analyses

A series of chi-square analyses were conducted between the variables age, gender, ART regimen type, transferred in, intervention (independent variable), side effects (i.e., lipodystrophy, lactic acidosis, and peripheral/poly neuropathy), concurrent illnesses (i.e., tuberculosis, herpes zoster, kaposi sarcoma), first CD4 count, baseline CD4 count, current CD4 count, *z*-score viral load, and the two dependent variables: LTF at 6 and 12 months, to determine if there were any significant associations between the covariates and the dependent variables. The variables: gender, pregnancy, ART regimen type, transferred in, intervention, lipodystrophy, lactic acidosis, peripheral/poly neuropathy, tuberculosis, herpes zoster, kaposi sarcoma, and opt out

were coded as nominal and dichotomous. Similarly, the two dependent variables, LTF at 6 and 12 months were also coded as nominal and dichotomous. Associations between the nominal and dichotomous variables listed above, and the dependent variables were ascertained using chi-square (χ^2) and phi (φ) statistics. This was a slight deviation from the information included in chapter 3, which stated use of Spearman chi square. The variables: age, first CD4 count, baseline CD4 count, current CD4 count and *z*-score viral load were coded as nominal but were not dichotomous. Associations between these variables and the dichotomous dependent variables were determined using a chi-square (χ^2) and Cramer's V or Cramer's phi statistic (φ_c). Covariates found to be associated with the dependent variables with *p*-values of < 0.25 were included as predictor variables in the logistic regression models in an effort to answer the two study research questions. The following ranges for the phi and Crammer's V statistics were used to interpret the strength of associations/effect size between the independent/ covariate and the dependent variables (http://faculty.quinnipiac.edu/libarts/polsci/Statistics.html):

If phi (φ) =

+.70 or higher. Very strong positive relationship

+.40 to +.69. Strong positive relationship

+.30 to +.39. Moderate positive relationship

+.20 to +.29. Weak positive relationship

+.01 to +.19. No or negligible relationship

-.01 to -.19. No or negligible relationship

-.20 to -.29. Weak negative relationship

-.30 to -.39. Moderate negative relationship

-.40 to -.69. Strong negative relationship

-.70 or higher. Very strong negative relationship

If Cramer's V (φ_c) =

.25 or higher. Very strong relationship

.15 to .25. Strong relationship

.11 to .15. Moderate relationship

.06 to .10. Weak relationship

.01 to .05. No or negligible relationship

Results from the model chi square analyses for the full study sample are presented in Tables 9 and 10. Below are the relevant ($p < .25$) associations found. The independent variable, intervention, was negatively associated with LTF at 6 months, χ^2 (1, N = 1750) = 68.40, φ = -.20, $p < .001$ and at 12 months, χ^2 (1, N = 1750) = 29.43, φ = -.13, $p < .001$,suggesting that individuals in the comparison group had a higher chance of LTF versus individuals in the intervention group. However, the phi statistic indicated a weak association between the two variables. Gender was negatively associated with LTF at 6 months χ^2 (1, N = 1750) = 4.51, φ = -.05, $p < .05$, and with LTF at 12 months χ^2 (1, N = 1750) = 2.40, φ = -.04, $p < .25$, indicating that men had a higher chance of LTF. However, the phi statistic for both the outcomes indicated negligible or no association between gender and the two LTF outcomes. Pregnancy was positively associated with LTF at 6 months χ^2 (1, N = 1750) = 12.24, φ = .08, $p < .001$ and LTF at 12 months χ^2 (1, N = 1750) = 8.63, φ = .07, $p < .01$, indicating that pregnant women had a higher chance of LTF. However, the phi statistic for both the outcomes indicated negligible or no association between pregnancy and the LTF outcomes. ART regimen type was negatively

associated with LTF at 6 months χ^2 (1, N = 1750) = 9.14, φ = -.07, p < .01 and LTF at 12 months χ^2 (1, N = 1750) = 2.33, φ = -.04, p < .25, indicating that individuals on ART regimen 1 had a higher chance of LTF versus individuals on ART regimen 2. However, the phi statistic for both the outcomes indicated negligible or no association between ART regimen and the LTF outcomes. Individuals who had transferred in had a negative association with LTF at 6 months χ^2 (1, N = 1750) = 3.44, φ = -.04, p < .25, indicating that individuals who had initiated on ART at another site and transferred to the study site had a lower chance of LTF at 6 months. However, the phi statistic indicated negligible or no association between the two variables. Peripheral/poly neuropathy had a negative association with LTF at 12 months χ^2 (1, N = 1750) = 1.44, φ = -.03, p < .25, indicating that individuals with peripheral/poly neuropathy had a lower chance of LTF at 12 months. The phi statistic indicated negligible or no association between the two variables. Herpes Zoster had a negative association with LTF at 12 months χ^2 (1, N = 1750) = 1.66, φ = -.03, p < .25, indicating that individuals with herpes zoster had a lower chance of LTF at 12 months. The phi statistic indicated negligible or no association between the two variables. Opt out was positively associated with LTF at 12 months χ^2 (1, N = 1750) = 5.18, φ = .05, p < .05, indicating that individuals who had opted out of the intervention had a higher chance of LTF at 12 months. However, the phi statistic indicated negligible or no association between the two variables.

Age was positively associated with LTF at 6 months χ^2 (51, N = 1750) = 83.40, φ_c = .22, p < .01 and at 12 months χ^2 (51, N = 1750) = 65.03, φ_c = .19, p < .25, indicating that older individuals has a higher chance of LTF at both 6 and 12 months. The Cramer's V statistic indicated a strong association between the two variables. Current CD4 count was positively associated with LTF at 6 months χ^2 (702, N = 1750) = 743.15, φ_c = .65, p < .25 and LTF at 12

months χ^2 (702, N = 1750) = 746.66, φ_c = .65, p < .25, indicating that individuals with higher current CD4 count had a higher chance of LTF at 6 and 12 months. The Cramer's V statistic indicated a very strong positive association between the two variables. Current viral load was also positively associated with LTF at 6 months χ^2 (194, N = 1750) = 469.82, φ_c = .52, p < .001 and LTF at 12 months χ^2 (194, N = 1750) = 333.88, φ_c = .44, p < .001, indicating that individuals with higher viral load had a higher chance of LTF at 6 and 12 months. The Cramer's V statistic indicated a very strong positive association between the two variables.

Table 9
Associations Between Nominal and Dichotomous Variables and LTF at 6 and 12 months for the Entire Study Population (N = 1750)

	LTF 6 Months			LTF 12 Months		
	X^2	φ	p	X^2	φ	p
Intervention	68.40	-.20	.000	29.43	-.130	.000***
Gender	4.51	-.05	.03	2.40	-.04	.12^
Pregnancy	12.24	.08	.00	8.63	.04	.00**
Transferred in	3.44	-.04	.06	.10	-.01	.75
Current ART Regimen	9.14	-.07	.00	2.33	-.04	.13^
Lipodystrophy	.28	-.01	.60	.38	-.01	.534
Lactic Acidosis	.48	.02	.49	.15	-.01	.70
Peripheral/Poly Neuropathy	.016	.00	.90	1.44	-.03	.23^
Tuberculosis	.70	.02	.40	.05	-.00	.83
Herpes Zoster	.71	-.02	.40	1.66	-.03	.20^
Kaposi Sarcoma	.18	-.01	.67	.41	-.01	.52
Opt Out	.28	-.01	.60	5.18	.05	.02*

Note. ^p < .25; *p < .05; **p < .01; ***p < .001

Table 10
Associations Between Nominal Non-Dichotomous Variables and LTF at 6 and 12 months for the Entire Study Population (N = 1750)

	LTF 6 Months			LTF 12 Months		
	X^2	φ_c	p	X^2	φ_c	p
Age	83.37	.22	.00*	65.03	.19	.09^
First reported CD4	330.05	.43	.77	386.79	.47	.59
Baseline CD4	743.15	.65	.14^	325.01	.43	.83
Current CD4	469.82	.52	.000***	746.56	.65	.12^
Current viral load (*z*-score)	387.71	.47	.58	333.88	.44	.000***

Note. ^$p < .25$; *$p < .05$; **$p < .01$; ***$p < .001$

Chi square analyses were conducted for each of the six cohorts to examine which covariates were relevant predictors (p < .25), of LTF at 6 and/or 12 months in each cohort. The independent variable, intervention as well as any covariates that were found to be correlated ($p <$ .25) to LTF at 6 and/or 12 months were included in the subsequent cohort level logistic regression models. In addition, baseline CD4 count was included in each of the cohort level regression models based on studies found in the literature, which found correlations between this covariate and LTF (Larson et al, 2010; Dalal et al, 2007).

Results for Cohort 1

Testing of covariates. Results from the model chi square analyses for cohort 1 are presented in Tables 11 and 12. Below are the relevant ($p < .25$) associations found. The independent variable, intervention, was negatively associated with LTF at 6 months, χ^2 (1, N = 195) = 3.42, φ = -.13, p = .06 and at 12 months, χ^2 (1, N=195) = 2.50, φ = -.11, p = .11, suggesting that individuals in the comparison group had a higher chance of LTF versus

individuals in the intervention group. However, the phi statistic fell in the category of negligible or no association between the two variables. Transferred in was positively associated with LTF at 12 months, χ^2 (1, N=195) = 2.14, φ = .10, p = .14, indicating that individuals in cohort 1, who initiated on ART at another facility and transferred into the study site had a higher chance of being LTF at 12 months. The phi statistic indicated negligible or no association between the two variables.

Baseline CD4 was positively associated with LTF at 6 months χ^2 (134, N = 195) = 151.23, φ_c = .88, p = .15, indicating that individuals with higher baseline CD4 count had a higher chance of LTF at 6 months. The Cramer's V statistic indicated a very strong association between the two variables. Current viral load was also positively associated with LTF at 6 months χ^2 (27, N=195) = 32.50, φ_c = .87, p = .21, indicating that individuals with higher viral load had a higher chance of LTF at 6 months. The Cramer's V statistic indicated a very strong association between the two variables.

Table 11
Cohort 1: Associations Between Nominal Dichotomous Variables and LTF at 6 and 12 Months (N = 195)

	LTF 6 Months			LTF 12 Months		
	X^2	φ	p	X^2	φ	p
Intervention	3.42	-.13	.06^	2.50	.11	.11^
Gender	.42	.05	.51	.22	-.03	.64
Pregnancy	.84	.06	.36	.06	.02	.81
Transferred in	.48	-.05	.49	2.14	-.10	.14^
Current ART Regimen	.64	-.06	.42	1.28	-.08	.26
Peripheral/Poly Neuropathy	.16	.03	.69	.31	-.04	.58
Tuberculosis	.09	.02	.76	.37	.04	.54
Herpes Zoster	.73	-.06	.39	.04	-.01	.84
Opt Out	n/a	n/a	n/a	n/a	n/a	n/a

Note. ^p <.25; *p < .05; **p < .01; ***p < .001

Table 12
Cohort 1: Associations Between Nominal Non-Dichotomous Variables and LTF at 6 and 12 Months (N = 195)

	LTF 6 Months			LTF 12 Months		
	X^2	φ_c	p	X^2	φ_c	p
Age	42.46	.47	.28	38.99	.45	.42
First reported CD4	144.98	.86	.58	141.35	.85	.66
Baseline CD4	151.23	.88	.15^	126.26	.80	.67
Current CD4	147.61	.87	.52	155.15	.89	.35
Current viral load (z-score)	32.50	.41	.21^	30.21	.39	.30

Note. ^$p < .25$; *$p < .05$; **$p < .01$; ***$p < .001$.

Logistic Regression. The first logistic regression for cohort 1 was conducted in relation to the dependent variable of 6-month loss to follow-up. Variables included in the model were the independent variable intervention, covariates found to be relevant associated ($p < .25$) with LTF at 6 months in the cohort 1 model chi-square analyses. In addition, baseline CD4 covariate was included in each regression model.

The results from the logistic regression are presented in Table 13. The model chi-square was significant, χ^2 (3, N=195) = 8.53, p = .04, indicating that the independent variables significantly predicted LTF at 6 months in cohort 1. The non-significance of the Hosmer and Lemeshow chi-square test indicated that the data fit the model, χ^2 (8) = 8.60, p = .38. The classification table output for model 1 (which included the various predictor variables) correctly classified 93.3% of the 6-month loss to follow-up outcome. In comparison, the classification table for model 0 (the model without the various predictor variables) indicated that the independent variable - intervention without the confounders correctly classified 92.8% of the 6 – month loss to follow up outcomes. There was a minimal difference in the classification tables between model 0 and 1. The Nagelkerke R^2 indicated 10.6% variance in the model.

Two variables significantly predicted ($p < .05$), 6-month loss to follow-up. Intervention group classification was significant, *Wald* (1) = 3.95, p = .04. The negative correlation with the outcome and odds ratio (*Exp B*) of .22 indicated that the odds of LTF at 6 months among individuals in the intervention group were .22 times less compared to individuals in the comparison group. Additionally, current viral load (z-score) was a significant predictor for LTF

at 6 month in cohort 1, *Wald* (1) = 5.37, p = .02. The odds ratio indicated that increases in viral load increased the odds of LTF at 6 months by 1.24 times.

Table 13
Cohort 1: Intervention and Predictor Variables for 6 Month LTF (N = 195)

	B	*SE B*	*Wald*	*p*	*Exp(B)*	*95% CI*	
						Low	*High*
Constant	-2.25	.58	14.82	.000	.10		
Intervention	-1.53	.77	3.95	.04*	.22	.05	.98
Baseline CD4	.000	.003	.02	.88	1.00	.99	1.01
Current Viral Load	.21	.09	5.37	.02*	1.24	1.03	1.48
χ^2	8.53						
Df	3						
Correct Classified	93.3						

Note. ^p < .25; *p < .05; **p < .01; ***p < .001.

The second logistic regression for cohort 1was conducted with regards to the dependent variable of 12-month loss to follow-up. As with the first logistic regression, variables included in the model were the independent variable – intervention and covariates found to be associated (p < .25) with LTF at 12 months in the cohort 1 model chi-square analyses. In addition, baseline CD4 covariate was included in each regression model. The results from the logistic regression are presented in Table 14. The model chi-square was not significant, χ^2 (3, N=195) = 4.27, p = .23, indicating that the independent and covariate variables did not significantly predict LTF at 12 months in cohort 1.

Table 14
Cohort 1: Intervention and Predictor Variables for 12 Month LTF (N = 195)

	B	*SE B*	*Wald*	*p*	*Exp(B)*	*95% CI*	
						Low	*High*
Constant	-1.49	.44	11.54	.001	.22		
Intervention	-.69	.45	2.32	.13	.50	.21	1.22
Transferred in	1.17	.90	1.67	.20	.50	.21	1.22
Baseline CD4	-.001	.002	.22	.64	.99	.99	1.00
χ^2	4.27						
Df	3						
Correct Classified	86.7%						

Note. ^p <.25; *p < .05; **p < .01; ***p < .001.

Analysis for Cohort 2.

Testing of Covariates. Results from the model chi square analyses for Cohort 2 are presented in Tables 15 and 16. Below are the relevant (p < .25) associations found. The independent variable, intervention, was negatively associated with LTF at 6 months, χ^2 (1, N = *238*) = 7.33, φ = -.17, p = .01 and at 12 months, χ^2 (1, N = *238*) = 4.79, φ = -.14, p = .03, suggesting that individuals in the comparison group had a higher chance of LTF versus individuals in the intervention group. However, the phi statistic at both 6 and 12 months LTF outcomes indicated negligible or no association between the two variables. Pregnancy was positively associated with LTF at 6 months χ^2 (1, N = 238) = 11.41, φ = .22, p = .001 and at 12 months, χ^2 (1, N=238) = 9.22, φ = .20, p = .002, indicating that pregnant women had a higher

chance of LTF at 6 and 12 months. However, the phi statistic at both 6 and 12 months LTF outcomes indicated a weak association between the two variables. The covariate, herpes zoster had a significant negative association with LTF at 12 months, χ^2 (1, N = 238) = 1.39, φ = -.08, p = .24, indicating that individuals in cohort who had herpes zoster had a lower chance of LTF at 12 months. However, the phi statistic indicated negligible or no association between the variables.

Age was positively associated with LTF at 6 months χ^2 (37, N=238) = 42.50, φ_c = .42, p = .25, indicating that older individuals had a higher chance of LTF at 6 months. The Cramer's V statistic indicated a strong association between the two variables. Baseline CD4 count was positively associated with LTF at 12 months, χ^2 (131, N=238) = 142.22, φ_c = .77, p = .24, indicating that individuals in cohort 2 with higher baseline CD4 count had a higher chance of LTF at 12 months. The Cramer's V statistic indicated a very strong association between the two variables. Current viral load was also positively associated with LTF at 6 months χ^2 (32, N = 238) = 43.89, φ_c = .43, p = .078 and at 12 months, χ^2 (32, N = 238) = 39.21, φ_c = .41, p = .18, indicating that individuals with higher viral load had a higher chance of LTF at 6 and 12 months. The Cramer's V statistic indicated a strong association for between the two variables at both the 6 and 12 months outcomes.

Table 15
Cohort 2. Associations Between Nominal Dichotomous Variables and LTF at 6 and 12 Months (N = 238)

	LTF 6 Months			LTF 12 Months		
	X^2	φ	p	X^2	φ	p
Intervention	7.32	-.17	.007**	4.79	-.14	.03*
Gender	.82	-.06	.36	.12	-.02	.73
Pregnancy	11.41	.22	.001**	9.22	.20	.002**
Transferred in	.22	-.03	.64	1.04	-.07	.31
Current ART Regimen	.44	-.04	.51	.02	.01	.88
Peripheral/Poly Neuropathy	.06	-.02	.81	.59	-.05	.44
Tuberculosis	.06	.02	.80	.00	-.00	.97
Herpes Zoster	.88	-.06	.36	1.39	-.08	.24^

Note. ^$p < .25$; *$p < .05$; **$p < .01$; ***$p < .001$.

Table 16
Cohort 2: Associations Between Nominal Non-Dichotomous Variables and LTF at 6 and 12 Months (N = 238)

	LTF 6 Months			LTF 12 Months		
	X^2	φ_c	p	X^2	φ_c	p
Age	42.50	.42	.25^	41.88	.42	.27
First reported CD4	143.83	.78	.71	153.58	.80	.49
Baseline CD4	125.07	.72	.63	142.22	.77	.24^
Current CD4	193.88	.90	.53	193.83	.90	.53
Current viral load (*z*-score)	43.89	.43	.08^	39.21	.41	.18^

Note. ^$p <.25$; *$p<.05$; **$p < .01$; ***$p < .00$.

Logistic Regression. Similar to Cohort 1 analyses, the first logistic regression was conducted with regards to the dependent variable of 6-month loss to follow-up for Cohort 2. Variables: intervention, pregnancy, age, baseline CD4 count, and current viral levels were included in the regression model. The results from the logistic regression are presented in Table 17. The model chi-square was significant, χ^2 (5, N = 238) = 16.10, p =.01, indicating that the independent variables significantly predicted LTF at 6 months in Cohort 2. The non-significance of the Hosmer and Lemeshow chi-square test confirmed that the data fit the model, χ^2 (8) = 4.41, p = .82. The classification table output for model 1 (which included the various predictor variables) correctly classified 86.1% of the 6 month – loss to follow up outcome. The classification table for model 0 (the model without the various predictor variables) indicated that the independent variable - intervention without the confounders correctly also classified 86.1% of the 6 – month loss to follow up outcomes. The Nagelkerke R^2 indicated 11.8% variance in the model.

Two variables were found to significantly ($p < .05$), predict 6-month loss to follow-up in Cohort 2. Intervention group classification was significant, *Wald* (1) = 5.08, $p = .02$. The negative correlation with the outcome and odds ratio (*Exp B*) of .36 indicated that the odds of LTF at 6 months among individuals in the intervention group was .36 times less likely compared to individuals in the comparison group. Pregnancy was a significant predictor, *Wald* (1) = 7.20, $p = .01$. The odds of LTF at 6 months was 6.43 times higher among pregnant women.

Table 17
Cohort 2: Intervention and Predictor Variables for 6 Month LTF (N = 238)

	B	*S.E.*	*Wald*	*p*	*Exp(B)*	*95% CI for EXP(B)*	
						Lower	Upper
Constant	-1.46	1.06	1.89	.17	.23		
Intervention	-1.03	.46	5.08	.02	.36	.14	.87
Pregnancy	1.86	.69	7.20	.007	6.43	1.65	25.02
Age	-.00	.02	.004	.95	.99	.95	1.05
Baseline CD4 count	-.001	.002	.05	.82	.99	.99	1.00
Current Viral Load	.41	.32	1.68	.19	1.51	.81	2.83
χ^2	16.10**						
Df	5						
Correct Classified	86.1%						

Note. *$p < .05$; **$p < .01$; ***$p < .001$.

The second logistic regression was conducted with regards to the dependent variable of 12- month loss to follow-up. The results from the logistic regression are presented in Table 17. The model chi-square was significant, $\chi^2(5, N = 238) = 21.87$, $p = .001$, indicating that the independent variable significantly predicted LTF at 12 months in Cohort 2. The non-significance of the Hosmer and Lemeshow chi-square test indicated that the data fit the model, $\chi^2(8) = 4.395$, $p = .820$. The classification table output for model 1 (which included the various predictor variables) correctly classified 79.8% of the 12-month loss to follow-up outcome. In comparison, the classification table for model 0 (the model without the various predictor variables) indicated

that the independent variable - intervention without the confounders correctly classified 78.6% of the 12 – month loss to follow up outcomes. There was a minimal difference in the classification tables between model 0 and 1. The Nagelkerke R^2 indicated 13.6% variance in the model.

Only pregnancy status significantly predicted ($p < .05$) 12- month loss to follow-up among individuals in Cohort 2 *Wald* (1) = 7.02, $p = .01$. The odds of LTF at 12 months were 6.02 times higher among pregnant women.

Table 18
Cohort 2: Intervention and Predictor Variables for 12 Month LTF (N = 238)

	B	*S.E.*	*Wald*	*p*	*Exp(B)*	*95% CI*	
						Lower	*Upper*
Constant	-.74	.38	3.80	.05	.48		
Intervention	-.60	.35	2.89	.09	.55	.28	1.10
Pregnancy	1.79	.68	7.02	.01	6.02	1.60	22.71
Herpes Zoster	-22.37	15181.68	.00	.99	.00	.00	-
Baseline CD4	-.002	.002	1.11	.29	.99	.99	1.00
Current Viral Load	1.19	.62	3.70	.05	3.28	.98	10.99
χ^2	21.87**						
Df	5						
Correct Classified	79.8%						

Note. ^$p < .25$, *$p < .05$; **$p < .01$; ***$p < .001$.

Analysis for Cohort 3

Testing of Covariates. Results from the model chi square analyses for Cohort 3 are presented in Tables 19 and 20. Below are the relevant ($p < .25$) associations found. The independent variable, intervention, was negatively associated with LTF at 6 months, χ^2 (1,

N=161) = 3.59, φ = -.15, *p* = .06 and at 12 months, χ^2 (1, *N = 161*) = 1.59, φ = -.10, *p* = .21, suggesting that individuals in the comparison group had a higher chance of LTF versus individuals in the intervention group. However, the phi statistic at both 6 and 12 months LTF outcomes indicated negligible or no association between the two variables. Current ART regimen was negatively associated with LTF at 6 months χ^2 (1, *N*=161) = 2.48, φ = -.12, *p* = .11, indicating that individuals in Cohort 3 on ART regimen 1 had a higher chance of LTF at 6 months versus individuals on ART regimen 2. However, the phi statistic indicated negligible or no association between the two variables. Individuals in Cohort 3, who had initiated on ART at another facility and transferred into this clinic had a positive association with LTF at 12 months χ^2 (1, *N*=161) = 2.55, φ = .13, *p* = .11. However, the phi statistic indicated negligible to no association between the variables.

Age was positively associated with LTF at 12 months χ^2 (36, *N* = 161) = 43.25, φ_c = .52, *p* = .19, indicating that older individuals had a higher chance of LTF at 12 months. The Cramer's V statistic indicated a strong association between the two variables. Current viral load was positively associated with LTF at 6 months χ^2 (23, *N* = 161) = 50.18, φ_c = .56, *p* = .001 and at 12 months, χ^2 (23, *N* = 161) = 42.64, φ_c = .51, *p* = .008, indicating that individuals with higher viral load had a higher chance of LTF at 6 and 12 months. The Cramer's V statistic indicated a strong association between the two variables at both the 6 and 12 months outcomes.

Table 19
Cohort 3: Associations Between Nominal Dichotomous Variables and LTF at 6 and 12 Months (N = 161)

	LTF 6 Months			LTF 12 Months		
	X^2	φ	p	X^2	φ	p
Intervention	3.60	-.15	.06^	1.59	-.10	.21^
Gender	.16	-.03	.69	.02	.01	.89
Pregnancy	.22	.04	.64	.00	.00	.95
Transferred in	.07	.02	.79	2.55	.13	.11^
Current ART Regimen	2.48	-.12	.11^	.60	-.06	.44
Peripheral/Poly Neuropathy	.15	-.03	.70	.27	-.04	.61
Tuberculosis	.52	.06	.47	.04	.01	.85
Herpes Zoster	.46	-.05	.50	.82	-.07	.37

Note. ^$p < .25$; *$p < .05$; **$p < .01$; ***$p < .001$.

Table 20
Cohort 3: Associations Between Nominal Non-Dichotomous Variables and LTF at 6 and 12 Months (N = 161)

	LTF 6 Months			LTF 12 Months		
	X^2	φ_c	p	X^2	φ_c	p
Age	29.85	.43	.75	43.25	.52	.19^
First reported CD4	107.73	.82	.83	120.73	.87	.54
Baseline CD4	96.34	.77	.85	113.62	.84	.44
Current CD4	137.49	.92	.50	138.99	.93	.46
Current viral load (*z*-score)	50.18	.56	.001**	42.64	.51	.008**

Note. ^p <.25; *p<.05; **p < .01; ***p < .001.

Logistic Regression. The first logistic regression was conducted with regards to the dependent variable of 6-month loss to follow-up for **C**ohort 3. Variables: intervention, Current ART regimen, and current viral load were found to be correlated (p < .25) to LTF at 6 months in Cohort 3 so these were included in the regression model along with the covariate, baseline CD4 count. The results from the logistic regression are presented in Table 21. The model chi-square was significant, χ^2 (4, N = 161) = 18.42, p = .001, indicating that the independent and/or covariate variables significantly predicted LTF at 6 months in Cohort 3. The non-significance of the Hosmer and Lemeshow chi-square test indicated that the model adequately fit the data, χ^2 (8) = 7.45, p = .49. The classification table output for model 1 (which included the various predictor variables) correctly classified 88.2% of the 6 - month loss to follow-up outcome. In comparison, the classification table for model 0 (the model without the various predictor variables) indicated that the independent variable - intervention without the confounders correctly classified 87.0% of the 6 – month loss to follow up outcomes. There was a minimal difference in the classification tables between model 0 and 1. The Nagelkerke R^2 indicated 20.1% variance in the model. None of the variables in the regression model significantly predicted LTF at 6 months in Cohort 3.

Table 21
Cohort 3: Intervention and Predictor Variables for 6 Month LTF (N = 161)

	B	*SE B*	*Wald*	*p*	*Exp(B)*	*95% CI*	
						Low	*High*
Constant	41.79	6564.45	.00	.99	1.417E+18		
Intervention	-.96	.56	2.95	.09	.38	.13	1.14
ART regimen	-42.37	6564.45	.00	.99	.00	.00	-

Baseline CD4	-.01	.00	3.01	.083	.99	.99	1.00
Current Viral Load	1.57	.89	3.14	.08	4.83	.85	27.52
χ^2	18.42**						
Df	4						
Correct Classified	88.2						

Note. *$p < .05$; **$p < .01$; ***$p < .001$.

The second logistic regression was conducted with regards to the dependent variable – LTF at 12 months. Variables: intervention, transferred in, age and viral load were found to be correlated ($p < .25$) to LTF at 12 months in Cohort 3 so these were included in the regression model along with baseline CD4 count. The results from the logistic regression are presented in Table 22. The model chi-square was not significant, χ^2 (5) = 7.67, $p = .17$, indicating that the model was not significant and the independent and covariate variables did not significantly predict LTF at 12 months in cohort.

Table 22
Cohort 3: Intervention and Predictor Variables for 12 Months LTF (N = 161)

	B	*SE B*	*Wald*	*p*	*Exp(B)*	*95% CI*	
						Low	*High*
Constant	-.01	.99	.00	.99	.99		
Intervention	-.63	.42	2.27	.13	.53	.23	1.21
Age	-.02	.02	.51	.47	.98	.94	1.03
Transferred in	1.16	.66	3.13	.08	3.02	.88	11.63
Baseline CD4	-.00	.00	2.11	.15	.99	.99	1.00
Current Viral Load	.06	.12	.29	.59	1.06	.85	1.34
χ^2	7.67						
Df	5						
Correct Classified	77.6%						

Note. ^ p <.25; *p < .05; **p < .01; ***p < .001.

Analysis for Cohort 4

Testing of Covariates. Results from the model chi square analyses for Cohort 4 are presented in Tables 23 and 24. Below are the relevant (p < .25) associations found. The independent variable, intervention, was negatively associated with LTF at 6 months, χ^2 (1, N = 380) = 11.31, φ = -.17, p = .001 and at 12 months, χ^2 (1, N = 380) = 1.80, φ = -.07, p = .18, suggesting that individuals in the comparison group had a higher chance of LTF versus individuals in the intervention group. However, the phi statistic at both 6 and 12 months LTF outcomes indicated negligible or no association between the two variables. Gender was negatively associated with LTF at 6 months χ^2 (1, N = 380) = 2.82, φ = -.09, p = .09 and at 12 months χ^2 (1, N =380) = 1.96 φ = -.07, p = .16, indicating that in Cohort 4, women had a lower

chance of LTF at 6 and 12 months versus men. However, the phi statistic indicated a negligible or no association between the variables for both the outcomes.

Age was positively associated with LTF at 6 months χ^2 (39, N=380) = 50.55, φ_c = .36, p = .10, indicating that older individuals had a higher chance of LTF at 6 months. The Cramer's V statistic indicated a very strong association between the two variables. First CD4 count was positively associated with LTF at 6 months χ^2 (204, N = 380) = 223.60, φ_c = .77, p = .16, indicating that individuals with higher first CD4 count had a higher chance of LTF at 6 months. The Cramer's V statistic indicated a very strong association between the variables. Baseline CD4 count was positively associated with LTF at 6 months χ^2 (188, N = 380) = 206.67, φ_c = .74, p = .17, indicating that individuals with higher baseline CD4 count had a higher chance of LTF at 6 months. The Cramer's V statistic indicated a very strong association between the variables. Current CD4 count was positively associated with LTF at 6 months, χ^2 (288, N = 380) = 334.16, φ_c = .94, p = .03, indicating that individuals in Cohort 2 with higher baseline CD4 count had a higher chance of LTF at 12 months. The Cramer's V statistic indicated a very strong association between the two variables. Current viral load was also positively associated with LTF at 6 months χ^2(51, N=238) = 156.98 φ_c = .64, p < .001 and at 12 months, χ^2 (51, N = 238) = 77.35, φ_c = .45, p = .01, indicating that individuals with higher viral load had a higher chance of LTF at 6 and 12 months. The Cramer's V statistic indicated a very strong association between the two variables at both the 6 and 12 months outcomes.

Table 23
Cohort 4: Associations Between Nominal Dichotomous Variables and LTF at 6 and 12 Months (N = 380)

	LTF 6 Months			LTF 12 Months		
	X^2	φ	p	X^2	φ	p
Intervention	11.31	-.17	.001**	1.80	-.07	.18^
Gender	2.83	-.09	.09^	1.96	-.07	.161
Pregnancy	.33	.03	.56	.05	.011	.82
Transferred in	.26	-.03	.61	1.18	.06	.28
Current ART Regimen	.06	-.01	.80	.08	.01	.78
Peripheral/Poly Neuropathy	.31	-.03	.58	1.065	-.05	.30
Tuberculosis	.25	-.03	.62	.85	-.05	.36
Herpes Zoster	.12	-.02	.72	.42	-.03	.52

Note. ^p <.25; *p < .05; **p < .01; ***p < .001.

Table 24
Cohort 4: Associations Between Nominal Non-Dichotomous Variables and LTF at 6 and 12 months (N = 380)

	LTF 6 Months			LTF 12 Months		
	X^2	φ_c	p	X^2	φ_c	p
Age	50.55	.36	.10^	32.55	.29	.76
First reported CD4 mean	223.60	.77	.16^	191.21	.71	.73
Baseline CD4 mean	206.67	.74	.17^	180.26	.69	.64
Current CD4 mean	334.16	.94	.03*	288.26	.87	.48
Current viral load (*z*-score)	156.30	.64	.000***	77.35	.45	.01*

Note. ^p <.25; *p<.05; **p < .01; ***p < .001.

Logistic Regression. The first logistic regression for Cohort 4 was conducted with regards to the dependent variable of 6- month LTF. Variables: intervention, age, gender, opt out, first CD4 count, baseline CD4 count, current CD4 count and current viral load were found to be correlated ($p < .25$) to LTF at 6 months in Cohort 4 so these were included in the regression model. The results from the logistic regression are presented in Table 25. The model chi-square was significant, χ^2 (7, $N = 380$) = 34.43, $p < .001$, indicating that the independent and/or covariate variables significantly predicted LTF at 6 months in Cohort 4. The non-significance of the Hosmer and Lemeshow chi-square test indicated that the model adequately fit the data, χ^2 (8) = 7.49, $p = .48$. The classification table output for model 1 (which included the various predictor variables) correctly classified 93.9% of the 6-month loss to follow-up outcome. In comparison, the classification table for model 0 (the model without the various predictor variables) indicated that the independent variable - intervention without the confounders correctly classified 94.2% of the 6 – month loss to follow up outcomes. There was a minimal difference in the classification tables between model 0 and 1. The Nagelkerke R^2 indicated 24.2% variance in the model.

Three variables significantly predicted ($p < .05$), 6-month loss to follow-up in Cohort 4. Intervention group classification was significant, *Wald* (1) = 8.854, $p = .003$. The negative correlation with the outcome and the odds ratio (*Exp B*) of .15 indicated that the odds of LTF at 6 months among individuals in the intervention group was .15 times less likely compared to the individuals in the comparison group. Age was negatively correlated to 6 month LTF, *Wald* (1) = 3.94, $p = .04$, The odds ratio (Exp B) of .94 indicated that the odds of LTF at 6 months was marginally lower among older individuals in Cohort 4. Current CD4 was negatively correlated with LTF at 6 months, *Wald* (1) = 8.89, $p = .003$. The odds ratio (*Exp B*) of .99 indicated that the odds of LTF at 6 months marginally decreased with increases in current CD4 counts.

Table 25
Cohort 4: Intervention and Predictor Variables for 6 Month LTF (N = 380)

	B	*SE B*	*Wald*	*p*	*Exp(B)*	*95% CI*	
						Low	*High*
Constant	1.38	1.31	1.11	.29	3.98		
Intervention	-1.92	.65	8.85	.003**	.15	.04	.52
Gender	-1.13	.61	3.39	.07	.32	.09	1.08
Age	-.06	.03	3.94	.04*	.94	.88	.99
First CD 4	-.01	.01	.42	.51	.99	.98	1.01
Baseline CD4	.01	.01	1.60	.21	1.01	.99	1.03
Current CD4	-.01	.00	8.90	.003**	.99	.99	.99
Current Viral Load	.43	.31	1.88	.17	1.53	.83	2.83
χ^2	34.43***						
Df	7						
Correct Classified	93.9						

Note. *$p < .05$; **$p < .01$; ***$p < .001$.

The second logistic regression for Cohort 4 was conducted with regards to the dependent variable of 12- month loss to follow up. Variables: intervention and current viral load were found to be correlated ($p < .25$) to LTF at 12 months in Cohort 4 so these were included in the regression model along with baseline CD4 count. Results from the logistic regression are presented in Table 26. The model chi-square was significant, χ^2 (3, N=380) = 9.24, p = .03, indicating that the independent variables significantly predicted LTF at 12 months in Cohort 4. The non-significance of the Hosmer and Lemeshow chi-square test confirmed that the data fit the model, χ^2 (8) = 5.89, p = .66, meaning that the model appropriately predicted the outcome. The classification table output for model 1 (which included the various predictor variables) correctly

classified 82.6% of the 12-month loss to follow-up outcome. In comparison, the classification table for model 0 (the model without the various predictor variables) also indicated that the independent variable - intervention without the confounders correctly classified 82.6% of the 12 – month loss to follow up outcomes. There was no difference in the classification tables between model 0 and 1. The Nagelkerke R^2 identified 4.0% variance in the model.

One variable significantly predicted ($p < .05$), 12-month loss to follow-up. Baseline CD4 count was positively correlated to the LTF outcome, *Wald* (1) = 4.51, $p = .03$. However, the 95% confidence interval for baseline CD4 included 1.00, thus the odds ratio was not significant.

Table 26
Cohort 4: *Intervention and Predictor Variables for 12 Month LTF* (N = 380)

	B	*SE B*	*Wald*	*p*	*Exp(B)*	*95% CI*	
						Low	*High*
Constant	-1.89	.30	39.15	.000	.151		
Intervention	-.36	.28	1.66	.20	.70	.40	1.21
Baseline CD4	.00	.00	4.51	.03	1.00	1.00	1.01
Current Viral Load	.46	.24	3.71	.05	1.58	.99	2.51
χ^2	9.24*						
Df	3						
Correct Classified	82.6						

Note. ^p <.25; *p < .05; **p < .01; ***p < .001.

Analysis for Cohort 5.

Testing of Covariates. Results from the model chi square analyses for Cohort 5 are presented in Tables 27 and 28. Below are the relevant ($p < .25$) associations found. The independent variable, intervention, was negatively associated with LTF at 6 months, χ^2 (1, N = 393) = 21.19, φ = -.23, p = .000 and at 12 months, χ^2 (1, N = 393) = 6.77, φ = -.13, p = .01, suggesting that individuals in the comparison group had a higher chance of LTF versus individuals in the intervention group. However, the phi statistic at 6 month indicated a weak association while the phi statistic at 12 months LTF indicated a negligible or no association between the variables. Current ART regimen had a negative association with LTF at 6 months χ^2 (1, N = 393) = 7.04, φ = -.134, p = .01, and with LTF at 12 months χ^2 (1, N = 393) = 3.53, φ = -.09, p = .06 indicating individuals on ART regimen 1 had a higher chance of LTF compared to individuals on ART regimen 2. The phi statistic indicated a negligible or no association between the variables for both the outcomes. Opt out was positively associated with LTF at 12 months χ^2 (1, N = 393) = 1.72, φ = .07, p = .19 indicating that individuals who had opted out of the intervention had a higher chance of LTF at 12 months compared to individuals who had stayed enrolled in the intervention. However, the phi statistic indicated a negligible or no association between the two variables.

Current CD4 count was associated with LTF at 6 months χ^2 (305, N =3 93) = 335.06, φ_c = .92, p = .11, indicating that individuals with a higher current CD4 count had a higher chance of LTF at 6 months. The Cramer's V statistic indicated a very strong association between the two variables. Current viral load was associated with LTF at 6 months χ^2 (53, N=393) = 43.89, φ_c =

.63, p = .000 and at 12 months, χ^2 (53, N=393) = 115.20, φ_c = .54, p = .000, indicating that individuals with higher viral load had a higher chance of LTF at 6 and 12 months. The Cramer's V statistic indicated a very strong association for between the two variables at both the 6 and 12 months outcomes.

Table 27
Cohort 5: Associations Between Nominal Dichotomous Variables and LTF at 6 and 12 months (N = 393)

	LTF 6 Months			LTF 12 Months		
	X^2	φ	p	X^2	φ	p
Intervention	21.19	.23	.000***	6.77	-.13	.01*
Gender	.26	-.03	.61	.43	-.03	.51
Pregnancy	.12	-.02	.73	.74	.04	.39
Transferred in	.11	-.02	.74	1.25	.06	.26
Current ART Regimen	7.04	-.13	.01*	3.53	-.09	.06^
Peripheral/Poly Neuropathy	.34	-.03	.56	.70	-.04	.40
Tuberculosis	.36	.03	.55	.02	-.01	.90
Herpes Zoster	.27	-.03	.60	.58	-.04	.45
Opt Out	.18	-.02	.67	1.72	.07	.19^

Note. ^p <.25; *p < .05; **p < .01; ***p < .001.

Table 28
Cohort 5: Associations Between Nominal Non-Dichotomous Variables and LTF at 6 and 12 months (N = 393)

	LTF 6 Months			LTF 12 Months		
	X^2	φ_c	p	X^2	φ_c	p
Age	26.20	.28	.96	37.90	.31	.61
First reported CD4 mean	194.56	.70	.81	206.87	.73	.60
Baseline CD4 mean	175.19	.67	.77	191.07	.70	.46
Current CD4 mean	335.06	.92	.11^	308.80	.89	.43
Current viral load (*z-score*)	154.80	.63	.000***	115.20	.54	.000***

Note. ^p <.25; *p<.05; **p < .01; ***p < .001.

Logistic Regression. The first logistic regression for Cohort 5 was conducted with regards to the dependent variable of 6-month loss to follow-up. Variables: intervention, current ART regimen, baseline CD4, current CD4, and current viral load were found to be correlated (p < .25) to LTF at 6 months in Cohort 5, so these were included in the regression model. Results from the logistic regression are presented in Table 29. The model chi-square was significant, χ^2 (5) = 39.79, p < .001 indicating that the independent variables significantly predicted LTF at 6 months in Cohort 5. The non-significance of the Hosmer and Lemeshow chi-square test confirmed that the data did fit the model, χ^2 (8) = 12.45, p = .13 and the model could predict the outcomes well. The classification table output for model 1 (which included the various predictor variables) correctly classified 91.9% of the 6-month loss to follow-up outcome. In comparison, the classification table for model 0 (the model without the various predictor variables) also indicated that the independent variable - intervention without the confounders correctly classified

91.9% of the 6 – month loss to follow up outcomes. The Nagelkerke R^2 suggested 22.3% variance in the model.

Three variables significantly predicted 6-month loss to follow-up in Cohort 5. Intervention was correlated with LTF at 6 months, *Wald* (1) = 13.76, $p < .001$. The negative correlation with the outcome and odds ratio (*Exp B*) of .10 indicated that the odds of LTF at 6 months among individuals in the intervention group were .10 times less likely compared to the individuals in the comparison group. Current ART regimen was also correlated with LTF at 6 months, *Wald* (1) = 3.90, $p = .04$. The negative correlation with the outcome and the odds ratio (*Exp B)* of .13 indicated that the odds of LTF at 6 months among individuals on ART regimen 2 was .13 times less likely compared to individuals on ART regimen 1. Current CD4 was negatively correlated with LTF at 6 months, *Wald* (1) = 4.56, $p = .03$. The odds ratio (*Exp B*) of .99 indicated that the odds of LTF at 6 months marginally decreased with increases in current CD4 counts. However, the upper bound of 95% confidence interval for baseline CD4 included 1.00, thus the odds ratio was not significant.

Table 29
Cohort 5: Intervention and Predictor Variables for 6 Month LTF (N = 393)

	B	*SE B*	*Wald*	*p*	*Exp(B)*	*95% CI*	
						Low	*High*
Constant	1.44	1.17	1.52	.22	4.23		
Intervention	-2.30	.62	13.76	.000***	.100	.03	.34
ART Regimen	-2.05	1.04	3.90	.04*	.129	.017	.985
Baseline CD4	.00	.00	.00	.99	1.00	.99	1.01
Current CD4	-.00	.00	4.56	.03*	.99	.99	1.00
Current Viral Load	.06	.21	.07	.79	1.06	.70	1.59
χ^2	39.79***						
Df	5						
Correct Classified	91.9						

Note. ^p<.25;*p < .05; **p < .01; ***p < .001.

The second logistic regression for Cohort 5 was conducted with regards to the dependent variable of 12-month loss to follow. Variables, intervention, current ART regimen, opt out and current viral load were found to be correlated (p < .25) to LTF at 6 months in Cohort 5 so these were included in the regression model along with baseline CD4 count.. The results from the logistic regression are presented in Table 30. The model chi-square was significant, χ^2 (5, N=393) = 21.89, p = .001, indicating that for Cohort 5, the independent variables significantly predicted the outcome of LTF at 12 months. The non-significance of the Hosmer and Lemeshow chi-square test confirmed that the data fit the model, χ^2 (8) = 5.56, p = .70, so the model could

predict the outcome appropriately. The classification table output for model 1 (which included the various predictor variables) correctly classified 85% of the 12-month loss to follow-up outcome. In comparison, the classification table for model 0 (the model without the various predictor variables) indicated that the independent variable - intervention without the confounders correctly classified 84% of the 12 – month loss to follow up outcomes. There was minimal difference in the classification tables between model 0 and 1. The Nagelkerke R^2 showed a 9.3% variance in the model.

Two variables significantly predicted 12-month loss to follow-up among individuals in Cohort 5. Intervention group classification was significant, *Wald* (1) = 5.51, p = .019. The negative correlation with the outcome and odds ratio (*Exp B*) of .50 indicated that the odds of LTF at 12 months among individuals in the intervention group were .50 times less likely compared to the individuals in the comparison group. Current viral load was a significant predictor for LTF at 12 month, *Wald* (1) = 5.49, p = .02. The odds ratio indicated that increases in viral load increased the odds of LTF at 6 months by 2.63 times.

Table 30
Cohort 5: Intervention and Predictor Variables for 12 Month LTF (N = 393)

	B	*SE B*	*Wald*	*P*	*Exp(B)*	*95% CI*	
						Low	*High*
Contrast	-.40	.55	.53	.47	.67		
Intervention	-.70	.30	5.51	.02	.50	.28	.89
Current ART Regimen	-.82	.43	3.68	.06	.44	.20	1.02
Opt Out	2.39	1.60	2.23	.13	10.90	.48	249.81
Base CD4 count	.00	.00	.00	.95	1.00	.99	1.00
Current viral load	.97	.41	5.49	.02	2.63	1.17	5.92
χ^2	21.89**						
Df	5						
Correct Classified	85%						

Note. $*p < .05$; $**p < .01$; $***p < .001$.

Analysis for Cohort 6.

Testing of Covariates. Results from the model chi square analyses for Cohort 6 are presented in Tables 31 and 32. Below are the relevant ($p < .25$) associations found. The independent variable, intervention, was negatively associated with LTF at 6 months, χ^2 (1, N = 382) = 26.75, φ = -.26, p = .000 and at 12 months, χ^2 (1, N = 382) = 15.50, φ = -.20, p = .000, suggesting that individuals in the comparison group had a higher chance of LTF versus individuals in the intervention group. The phi statistic at both 6 and 12 months LTF outcomes indicated a weak association between the two variables. Gender was negatively correlated with LTF at 6 months, χ^2 (1, N = 382) = 5.55, φ = -.12, p = .02, indicating that females in Cohort 6

had a lower chance of LTF at 6 months versus males. Pregnancy was positively associated with LTF at 6 months χ^2 (1, N = 382) = 10.81, φ = .17, p = .001 and at 12 months, χ^2 (1, N = 382) = 5.75, φ = .12, p = .02, indicating that pregnant women had a higher chance of LTF at 6 and 12 months. However, the phi statistic for both 6 and 12 months LTF outcomes indicated a negligible or no association between the two variables. Transferred in has a negative association with LTF at 6 months, χ^2 (1, N = 382) = 1.42, φ = -.06, p = .23, indicating that individuals who had initiated on ART at another clinic and transferred into the study clinic had a lower chance of LTF at 6 months. However, the phi statistic indicated a negligible or no association. Peripheral/ poly neuropathy had a positive association with LTF at 6 months, χ^2 (1, N = 382) = 2.45, φ = .08, p = .12, indicating that individuals in cohort 6 who had peripheral/poly neuropathy had a higher chance of LTF at 6 months versus individuals who did not have peripheral/poly neuropathy. However, the phi statistic indicated negligible or no association between the variables. Herpes Zoster had a positive association with LTF at 6 months, χ^2 (1, N = 382) = 2.25, φ = .08, p = .13, indicating that individuals in Cohort 6 who had herpes zoster had a higher chance of LTF at 6 months versus individuals who did not have herpes zoster. However, the phi statistic indicated negligible or no association between the variables. Opt out was positively associated with LTF at 12 months, χ^2 (1, N = 382) = 5.38, φ = .12, p = .02, indicating that individuals in Cohort 6 who had opted out of the intervention had a higher chance of LTF at 12 months versus individuals who did not opt out of the intervention. However, the phi statistic indicated negligible or no association between the variables.

Current CD4 count was positively associated with LTF at 6 months, χ^2 (300, N=382) = 324.77, φ_c = .92, p = .16, indicating that individuals in Cohort 6 with higher current CD4 count had a higher chance of LTF at 6 months. The Cramer's V statistic indicated a very strong

association between the two variables. Current viral load was also positively associated with LTF at 6 months χ^2 (60, N=382) = 152.57, φ_c = .63, p = .000 and at 12 months, χ^2 (60, N=382) = 106.03, φ_c = .53, p = .000 indicating that individuals with higher viral load had a higher chance of LTF at 6 and 12 months. The Cramer's V statistic indicated a strong association for between the two variables at both the 6 and 12 months outcomes.

Table 31
Cohort 6: Associations Between Nominal Dichotomous Variables and LTF at 6 and 12 months (N = 382)

	LTF 6 Months			LTF 12 Months		
	X^2	φ	p	X^2	φ	p
Intervention	26.75	-.26	.000***	15.50	-.20	.000***
Gender	5.55	-.12	.02*	.86	-.05	.35
Pregnancy	10.81	.17	.001**	5.75	.12	.02*
Transferred in	1.42	-.06	.23^	4.74	-.11	.03*
Current ART Regimen	.16	-.02	.69	.02	-.01	.88
Peripheral/Poly Neuropathy	2.45	.08	.12^	.02	.01	.88
Tuberculosis	.35	-.03	.55	.94	.05	.33
Herpes Zoster	2.25	.077	.13^	.26	.03	.61
Opt Out	.07	-.01	.79	5.38	.12	.02*

Note. ^p <.25; *p < .05; **p < .01; ***p < .001.

Table 32
Cohort 6: Associations Between Nominal Non-Dichotomous Variables and LTF at 6 and 12 months (N = 382)

	LTF 6 Months			LTF 12 Months		
	X^2	φ_c	p	X^2	φ_c	p
Age	24.73	.25	.98	31.72	.29	.85
First reported CD4	171.93	.67	.61	159.45	.65	.84
Baseline CD4	163.78	.66	.49	153.76	.63	.71
Current CD4	324.76	.92	.16^	301.43	.89	.47
Current viral load (z-score)	152.57	.63	.000***	106.03	.53	.000***

Note. ^p <.25; *p<.05; **p < .01; ***p < .001

Logistic Regression. The first logistic regression for Cohort 6 was conducted with regards to the dependent variable of 6 month LTF. Variables: intervention, gender, pregnancy, transferred in, peripheral/poly neuropathy, herpes zoster, current CD4 count and current viral load were found to be associated (p < .25) with LTF at 6 months in Cohort 6 so these were included in the regression model along with baseline CD4. The results from the logistic regression are presented in Table 33. The model chi-square was significant, χ^2 (9) = 58.40, p < .001, indicating that the independent variables significantly predicted LTF at 6 months in Cohort 6. The non-significance of the Hosmer and Lemeshow chi-square test confirmed that the model adequately fit the data, χ^2 (8) = 3.19, p = .92. The classification table output for model 1 (which included the various predictor variables) correctly classified 94.2% of the 12-month loss to follow-up outcome. In comparison, the classification table for model 0 (the model without the various predictor variables) indicated that the independent variable - intervention without the confounders correctly classified 93.5% of the 12 – month loss to follow up outcomes. There was

a minimal difference in the classification tables between model 0 and 1. The Nagelkerke R^2 indicated 37.0% variance in the model.

Two variables significantly predicted 6 month LTF among Cohort 6. Gender was a significant predictor, *Wald* (1) = 4.42, *p* = .04. There was a negative correlation indicating that females were .223 times less likely to be LTF at 6 months compared to males. Pregnancy was a significant predictor, *Wald* (1) = 6.76, *p* = .01. Pregnant women were 24.44 times more likely to be LTF at 6 months follow-up.

Table 33
Cohort 6: Intervention and Predictor Variables for 6 Month LTF (N = 382)

	B	*SE B*	*Wald*	*p*	*Exp(B)*	*95% CI*	
						Low	*High*
Constant	-1.07	.73	2.16	.14	.34		
Intervention	-32.61	3256.49	.00	.99	.00	.00	-
Gender	-1.50	.71	4.42	.04*	.22	.05	.90
Pregnancy	3.20	1.23	6.75	.01*	24.44	2.19	272.25
Transferred in	.40	.52	.59	.44	1.50	.54	4.18
Peripheral/Poly Neuropathy	.26	.65	.16	.69	1.29	.36	4.65
Herpes Zoster	17.70	2321.63	.00	.99	48730578.22	.00	
Baseline CD4 count	.00	.00	.06	.81	1.00	.99	1.01
Current CD4 Count	-.00	.00	2.69	.10	.99	.99	1.00
Current Viral Load	.15	.12	1.65	.20	1.16	.92	1.47
χ^2	58.40***						

Df	9
Correct Classified	94.2

Note. ^*p*.25; *$p < .05$; **$p < .01$; ***$p < .001$

The second logistic regression for Cohort 6 was conducted with regards to the dependent variable of 12-month loss to follow-up. Variables: intervention, pregnancy, transferred in, opt out, and current viral load were found to be correlated ($p < .25$) to LTF at 12 months in Cohort 6 so these were included in the regression model along with baseline CD4 count.

The results from the logistic regression are presented in Table 34. The model chi-square was significant, χ^2 (6, 382) = 25.73, $p < .001$. The non-significance of the Hosmer and Lemeshow chi-square test confirmed that the data fit the model, χ^2 (8) = 6.78, $p = .56$. That is, the model predicted the outcome appropriately. The classification table output for model 1 (which included the various predictor variables) correctly classified 84.8% of the 12-month loss to follow-up outcome. In comparison, the classification table for model 0 (the model without the various predictor variables) indicated that the independent variable - intervention without the confounders correctly classified 84.3% of the 12 – month loss to follow up outcomes. There was a minimal difference in the classification tables between model 0 and 1. The Nagelkerke R^2 indicated 11.2% variance in the model.

One variable significantly predicted 12-month loss to follow-up among individuals in Cohort 6. Intervention was a significant predictor, *Wald* (1) = 12.24, $p < .001$. The negative correlation to the outcome and odds ratio (*Exp B*) of .31 indicated that individuals in the intervention group were .31 times less likely to be LTF at 12 months compared to the individuals in the comparison group.

Table 34
Cohort 6: Intervention and Predictor Variables for 12 Month LTF (N = 382)

	B	*SE B*	*Wald*	*p*	*Exp(B)*	*95% CI*	
						Low	*High*
Constant	-1.18	.28	17.58	.00	.31		
Intervention	-1.17	.33	12.24	.00	.31	.16	.60
Pregnancy	1.29	.79	2.68	.10	3.62	.78	16.89
Transferred in	-.30	.33	.79	.37	.74	.38	1.43
Opt out	22.28	40192.97	.00	1.0	4.74E+6	.00	.
Baseline CD4	.00	.00	.00	.99	1.00	.99	1.00
Current Viral Load	.12	.10	1.31	.25	1.12	.92	1.38
χ^2	25.73***						
Df	6						
Correct Classified	84.8%						

Note. ^p<.25; *p < .05; **p < .01; ***p < .001

Treatment and/or Intervention Fidelity

As mentioned in Chapter 3, the intervention was implemented as planned with the exception that all individuals enrolled in the appointment reminder intervention also received weekly adherence messages. This may be a major threat to the internal validity of the study as it is difficult to ascertain if the outcomes observed were a result of the appointment reminder or the weekly adherence messages that the individuals received in the intervention group. Additionally the full impact of combining the two interventions could not be ascertained by this study. There were no adverse events reported by the team.

Summary

In response to the two research questions, yes, there was a difference in 6 and/or 12-month LTF rates among patient enrolled in the appointment reminder intervention versus the comparison group in five out of six study cohorts. Regression analyses by each cohort indicated that individuals in Cohorts 1, 2, 4 & 5 had a lower likelihood of LTF at 6 months compared to individuals in the comparison group. Similarly, individuals in Cohorts 5 and 6 had a lower likelihood of LTF at 12 months compared to the individuals in the comparison group.

Other variables that had a positive or a negative correlation with LTF were pregnancy, age, gender, current ART regimen, current CD4 count, and current viral load. The independent and covariate variables significantly predicted LTF at 6 months for all the cohorts except for Cohort 3. In contrast, the independent and covariate variables significantly predicted 12 month LTF for Cohorts 2, 4, 5 & 6 only.

The next chapter includes a discussion of and conclusions based on the study findings. Limitations of the study, future recommendations for continued research, and the social change implications are also included in Chapter 5.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The purpose of this study was to evaluate the effectiveness of a mHealth patient appointment reminder intervention to improve retention in treatment of patients initiating ART at a large public sector ART clinic in the inner city of Johannesburg, South Africa. This clinic is one of the largest ART clinics located at a secondary-level community health facility in Sub-Saharan Africa, and it has a relatively heterogeneous population accessing HIV care and treatment. The appointment reminder intervention was one of three mHealth interventions developed, piloted, and scaled up at this and the surrounding primary health care clinics in the inner city of Johannesburg, in an effort to reduce the loss to follow up rates among patients on ART. The appointment reminder intervention was implemented at this clinic in September 2012. Individuals on ART at the clinic were approached and the intervention was offered to them. Individuals self-selected to participate in the project. This study was a program evaluation of the intervention based on a quantitative retrospective cohort design. Retrospective project and clinical data was used for this study for the period September 1, 2012 to January 31, 2014.

This study was conducted in an effort to find evidence if mHealth can be an effective way to reduce post-ART LTF. As mentioned in Chapter 2, currently there are only a few studies in the scientific literature, which look at the effectiveness of interventions to reduce LTF among patients on ART. Furthermore, since mHealth is an up and coming field, there is a gap in the literature on studies on the effectiveness of mHealth interventions in reducing LTF, especially in the context of Sub-Saharan Africa.

The two research questions for this study sought to ascertain whether there were differences in 6 and 12 - month LTF outcomes between the intervention and the comparison

groups. The analyses were based on the study design, which included assignment of individuals in the intervention and comparison groups to one of six cohorts, based on their time on ART when the intervention was implemented.

The study population was demographically representative of the clinic population. The mean age and gender disaggregation of the study population were found to be similar to the clinic population information reported in the HCHC file audit report from 2009 (unpublished report). The intervention and comparison groups were found to be similar in terms of gender and age. The study sample size was sufficient to provide responses to the study questions. Individuals in the intervention group were found to have less likelihood of LTF at 6 months in four of the six cohorts, and in two of the six cohorts for LTF at 12 months. Thus, the two null hypotheses were rejected for a subset of the study cohorts. In addition, current CD4 counts, pregnancy status and current viral load predicted LTF outcome among three cohorts. Age, gender, baseline CD4 count and ART regimen predicted either 6- or 12-month LTF outcome for one non-mutually exclusive cohort each.

Opt-out from the intervention was low - only eight - three of whom provided reasons: transfer to maternity clinic, recognition that the existing support was enough that reminders were not needed, concern about disclosure of HIV status.

Interpretation of the Findings

The study results indicated a significant correlation ($p < .05$), between enrollment in the intervention group and decreased likelihood of LTF at 6 and/or 12 months, compared to individuals in the comparison group in a subset of the six study cohorts. Other significant findings among a few of the study cohorts were the links between 6 and/or 12 month LTF and each of the covariates: pregnancy, current CD4 count and current viral load. Pregnant women

had a higher likelihood of LTF in four instances among three cohorts. Increases in current CD4 count were correlated with lower LTF outcome, and increases in viral load count were correlated with higher likelihood of LTF among individuals in three of the study cohorts for both of these covariates. Age, gender, current ART regimen and baseline CD4 count were correlated with 6 or 12 - month LTF outcomes in one cohort each, whereby, older individuals had a higher likelihood of LTF, women had a lower likelihood of LTF, and individuals on ART regimen 2 had a lower likelihood of LTF compared to individuals on ART regimen 1. Baseline CD4 count was found to be significantly correlated however the odds ratio was not significant.

The median baseline CD4 count of 137 cells/mm^3 indicated that the patients were being initiated on ART at the facility much later than the NDoH 2012 guidance to initiate individuals with CD4 <350 cells/mm^3 on ART within a short duration of HIV diagnosis, and to immediately initiate all children under 5 years, HIV pregnant women and any patients identified with tuberculosis, regardless of CD4 count. (South African National Strategic plan on HIV, STIs, and TB 2012-2016; South African HIV/AIDS treatment and PMTCT guidelines, 2011 and 2013). It was beyond the scope of this study to conduct in depth analyses on this issue and differentiate if the delay in ART initiation pertained to individuals who had been initiated on ART a while ago (Cohorts 3-6), or if it was also the case for individuals who had been recently initiated on ART (Cohorts 1-2). The median figure of 384 cells/mm^3 for the current CD4 count indicated that regardless of the baseline CD4 count, most of the individuals had an increase in their CD4 count after initiating ART. A large portion of individuals, who had recent viral load information in their records, had an undetectable viral load. Among individuals who had a detectable viral load, increases in viral load values were correlated with increases in the LTF outcomes in two cohorts. A majority of the individuals in the study were on ART regimen 1. Approximately, 20% of the

individuals had been switched to regimen 2, and the number of individuals on regimen 2 was higher for Cohorts 3-6 indicating an increase in ART regimen change with increase in time on ART. Approximately 11 % of the study sample experienced a side effect of lipodystrophy, lactic acidosis or peripheral/poly neuropathy during the study period. Similarly, 5% of the study population had a documented concurrent illness of tuberculosis, herpes zoster or kaposi sarcoma during the study period.

The appointment reminder intervention was significantly linked to lower likelihood of 6 and/or 12 months LTF among patients who had initiated on ART anywhere from a few days to a few years prior to enrolling in the intervention. In addition, there were a few covariates that also significantly impacted LTF outcomes among multiple study cohorts. The correlation between pregnancy and LTF was a key finding, and this correlation has been previously reported in the literature (Bateman, 2013; Clouse, 2013; Wang et al, 2011). The current South African guideline for Prevention of Mother to Child Transmission of HIV (PMTCT) includes providing HIV positive pregnant women who are not already on ART when they become pregnant, with antiretrovirals for the duration of the pregnancy up to one-year post pregnancy, to cover the one-year of breast feeding period. Some women may need to continue on ART for the rest of their lives if their CD4 count is <350 cell/mm^3 (Bateman, 2013). This study confirms the high risk of LTF outcome among pregnant women and highlights a need to adjust services provided to pregnant women.

The correlation between increases in viral loads and increased LTF is another key study finding. Annual viral load monitoring and informing the individuals of their viral load status via text messaging is a potential intervention that can be recommended to the NDoH to undertake.

This study confirms and adds evidence to the existing literature about the effectiveness of using mHealth-based interventions to improve HIV/AIDS care and treatment programs. As mentioned in Chapter 2, Bahadur & Murray, 2010 had conducted a review of publications to find the outcomes of SMS in health care settings. The authors concluded that a few studies that indicated that SMS had improved health service delivery through appointment reminders, however, most of the research was conducted in developed countries and most of them either reported on pilots or feasibility studies. A need was identified for studies that are conducted in low resource countries and/or which report on scaled up projects versus pilots. Another gap identified from the literature search was that there is a lack of studies, which examine the association or effectiveness of SMS on improving ART clinic appointment adherence among patients on ART in South Africa. This study meets the gaps mentioned above as it was conducted in a low resource setting, at a public sector ART site, and it was an evaluation of a project that had been implemented as a scale up following the success of an earlier pilot project. This study extends the knowledge base around use and effectiveness of mHealth based interventions in the field of HIV/AIDS.

Findings in the Context of the Theoretical Framework

As mentioned in Chapter 2, the theoretical framework that formed the basis of this study was the "cues to action" construct of the health belief model. The key question stated in Chapter 2, in terms of the theoretical framework was "How effective were the cues to action in leading to the desired behavior or intervention outcome?" The cues to action for this study were the appointment reminders sent to the individuals enrolled in the intervention. Some of the assumptions that were made before the study was conducted were that individuals who agreed to partake in the appointment reminder intervention perceived: the benefit of initiating ART and the

benefit that the intervention offered to them. The study data showed that the cues were effective in leading to reduction in LTF rates among the individuals enrolled in the intervention who received the cues, versus the individuals in the comparison group who only received the standard of care at the clinic. The low opt out rate from the intervention may indicate the perceived benefits and effectiveness of the cues too.

Limitations of the Study

The limitations to validity and reliability that arose from the execution of the study were in line with the expected limitations mentioned in chapter 1. A major limitation to this study was the change in the way the intervention was implemented versus the project plan. Instead of offering only the appointment reminder intervention to individuals newly (< 30 days) initiating ART, all individuals on ART (regardless of time on ART) were offered the appointment reminder intervention along with weekly treatment adherence reminder messages for one year. While this modification was based on the lessons learned, it potentially had an impact on the study outcomes. It was beyond the scope of this study to ascertain if the differences noted between the intervention and control groups were due to the appointment reminder or the adherence reminder intervention. An evaluation of the adherence reminder program may assist to distinguish the differences between the two interventions.

Another limitation of the study was the non-random selection of individuals to enroll in the intervention. The participants self-selected to receive the intervention, thus the risk of selection bias was valid. The comparison group was selected using a partly purposeful, partly random stratified approach in an effort to lower the effect of the selection bias among the individuals enrolled in the intervention group. The low difference found between the intervention and comparison group should have assisted in reducing the impact of the selection bias.

Another limitation of this study was that a quantitative method of inquiry was used for the evaluation. A mixed method would have been a more appropriate methodology as a qualitative component could have assisted in explaining some of the participant behavior, decisions or nuances leading to the outcomes noted. These items are not easy to ascertain from a quantitative methodology only. Furthermore, given the quantitative nature of this study, it was not possible to ascertain how the cues to action affected the perceptions of and led to behavior change among the individuals enrolled in the intervention. This is a limitation of the study and could be better answered via a qualitative inquiry.

Data quality was found to be less than ideal. Errors identified in the data included discrepancies in the ART initiation dates between the intervention database and the HMIS information available from the clinic. When the dates did not match, the information from the HMIS was used as that is the archived data used by the clinic. Similarly, if discrepancies were found in the "last visit date" information, which was the variable used to ascertain the LTF outcome, the information from the HMIS dataset was used versus the intervention database.

Other limitations as mentioned in Chapter 1, are still valid as they were beyond the researcher's control. Given the sheer size of the HIV epidemic in South Africa, HIV is the focus of the government, donors and other international agencies agendas. For example, the minister of health started country wide HIV counseling and testing campaigns in 2010. These campaigns are in their fourth year now and continue to be scaled up as still only 31% of the HIV positive individuals in South Africa are on ART (HSRC report, 2012). The South African public is constantly exposed to messages regarding HIV prevention, testing and treatment from the government, donors, non-government organizations, community based organizations and others. In addition, it is likely that given the high prevalence of HIV, a large proportion of the

population in South Africa has been affected by HIV directly or indirectly. Therefore, it is possible that the other experiences and exposures may act as cues to action for the study participants, and possibly drive the outcomes towards the null hypothesis.

A limitation that was identified in Chapter 1, but which did not have an effect on the study outcome was that the South African public has a tendency to change their cell phone numbers frequently so the intervention participants may not have received the messages as planned. In actuality, the project was able to successfully dispatch the appointment reminders to almost all the individuals enrolled in the intervention. The project implementers had instituted two interventions to reduce this issue. The first intervention pertained to instant verification, that is, when individuals enrolled in the intervention, the field workers immediately sent a verification message to make sure the number provided was correct. The second intervention involved asking the participants if their phone numbers had changed since the last clinic or pharmacy visit. The above two interventions may have been successful in making sure that the project always had the most up to date phone numbers for the individuals enrolled in the intervention.

Recommendations

Recommendations for Further Study

A recommendation based on the outcome of the study is that a qualitative inquiry should be conducted on the population enrolled in the intervention to find out: the reasons for individuals enrolling and continuing with the intervention, the reasons for the behavior change noted, which components of the intervention were most useful and which areas need improvement, and if the frequency and content of the text messages were sufficient or could be improved. Qualitative study will also assist in obtaining lessons learned, and ascertaining areas

of improvement or intervention strengths that could be incorporated in the project before scale up to other ART facilities.

While the results from this study can be generalized to other clinics in South Africa, there is a need for this type of intervention and follow up inquiry in a rural health care setting as a large proportion of individuals on ART in South Africa and other resource limited countries reside in rural areas. As mentioned in chapter 2, individuals in urban and rural settings may have different set of barriers, which may hinder retention in ART.

It is important to ascertain what impact the adherence reminder intervention which was implemented along with the appointment reminders had on the LTF outcomes. It would also be useful to follow up the patients beyond the 12 month period, ideally for 24 and 36 months to see if there are changes in LTF rates between the intervention and comparison groups over an extended period.

Recommendations for Action

The positive correlation between pregnancy and LTF is a key finding and requires adjustments in ART service delivery to this group of individuals. The outcome highlights the need to closely monitor pregnant women on ART both during and after their pregnancies to make sure that they continue to adhere to ART. Specific messaging either via text messages or in person counseling, which highlight the importance of treatment retention to pregnant women could be useful. Another option is to incorporate the messages in other Maternal and Child Health (MCH) related projects. One such instance is the MCH related mHealth project that was implemented at the MCH clinic located at the study site in 2012. In this project, women enrolled in the intervention receive weekly messages about their pregnancy, fetal growth, appropriate nutrition and other items, till the baby is a year old. Women who want messages regarding HIV

and pregnancy can opt in to receive these messages. At the end of 2014, the South African government asked for and received funding from USAID & CDC to scale up this MCH related mHealth project to all public sector sites in the country. Based on the evidence obtained from this evaluation, it would be useful for the NDoH to include importance of continuation of ART post pregnancy and appointment retention messages in this MCH project.

The positive correlation between increase in viral loads and LTF is another area indicating a need for modification in the public sector ART service delivery in South Africa. As mentioned above, annual viral load monitoring of patients on ART is recommended so that patients and the caregivers can monitor the patient's viral load. In addition to this, systems need to be put in place that raise a red flag to the clinician and other relevant clinic staff when the viral loads go from undetectable to detectable range. This is important in terms of monitoring development of ART drug resistance in the patient, identifying possible ART adherence issues, and providing additional counseling to patient to adhere to their ART appointment as they are at higher risk of LTF.

Given the high acceptability and feasibility of mHealth related interventions in South Africa, along with the evaluation outcomes, the appointment reminder intervention can be scaled up to other sites. In addition, other fields such as MCH, immunizations, and tuberculosis treatment could benefit from mHealth projects similar to the appointment reminder intervention as these health service areas require frequent visits to the clinic whether they are for pre-natal visits for MCH or immunizations which have to be given to children at specific ages or for TB which usually requires an intensive treatment regimen for six months or longer. Similar to ART, TB treatment is an area that requires the patients to be strictly adherent to the treatment regimen for it to be fully effective and to avoid development of drug resistance.

The appointment reminder interventions was funded by the US Government as a public private partnership grant in conjunction with the Vodacom Foundation – the not for profit division of Vodacom, one of the largest cell phone companies in Africa and Europe. Vodacom had provided subsidized rates for SMS messages for this intervention however, if the South African Government is going to take this and related mHealth interventions to scale in the country, then a cost effectiveness study needs to be conducted.

The next steps after the conclusion of this dissertation includes sharing of the information with the stakeholders including the host institution, individuals enrolled in the intervention, clinic leadership, funders of the mHealth projects and the South African NDoH. The results will be disseminated via a formal correspondence to the host institution to share with the NDoH and presented at public health conferences. The dissertation information will be used to develop an article for a peer-reviewed journal.

Implications

Positive Social Change

As stated in earlier chapters, the social change impact of this study is substantial at various levels. At the individual level, the intervention is an effective external cue to action that reminds and assists the individuals to adhere to their ART appointments. Some individuals found the appointment reminders motivating. Evidence of this was found from some anecdotal comments from the study staff, who stated that patients felt that “someone (clinic) cared about them”. Another instance was an example from the MCH mHealth project when a pregnant woman shared the weekly SMS message she received regarding her baby’s growth and other information for that week, with other women in the waiting room. This led to a surge in women wanting to enroll in the mHealth MCH project.

This intervention and the results from this study are important at the family level too as studies in the scientific literature, listed in chapter 2, have shown that adherence on ART and retention in care reduced the risk of HIV related complications and other illnesses. If the individual is healthy then they can provide for and support their family much better. At the organizational level, the results from this intervention and study can have a positive impact on the quality of the services provided by the clinic, and the funding of the services by the DoH. If individuals are adhering to their appointment date, the clinic can have improved scheduling leading to reduction in patient waiting times, and the clinic leadership can better plan for their ARV stocks. Since there is a lower chance of individuals developing treatment resistance when they are adherent on ART, the clinic can save on the costs of running some of the expensive viral resistance blood tests.

Loss to follow up is a major issue that the NDoH is struggling with in South Africa and the results of this study provide an evidence base for an innovative solution to reduce LTF. Appointment reminders can be included as standard of care and offered to all individuals initiating ART in the public sector. This study along with the feasibility, acceptability and pilot studies results provide compelling evidence that mHealth is an effective mode of reducing LTF and improving retention in care of individuals on ART. At the scientific community level, the results of this study provide evidence on the effectiveness of mHealth to reduce LTF in a low resource setting and in the field of HIV/AIDS. The results from this study will be useful to support some of the mandates of international policy organizations such as the Joint United Nations Programme on HIV/AIDS (UNAIDS) or for funding programs such as the President's Emergency Plan for AIDS Relief (PEPFAR). In the 2014 gap report, UNAIDS set an ambitious goal of 90/90/90 to end the HIV epidemic by 2020. That is, by 2020: 90% of all people living

with HIV will know their HIV status, 90% of all people diagnosed with HIV infection will receive ART, and 90% of all people receiving ART will have viral suppression. (UNAIDS Gap report, 2014). PEPFAR is currently in its third five-year cycle and the leadership has made 90/90/90 the main objective of PEPFAR 3. This intervention supports the third 90 in the 90/90/90 that is maintenance of viral suppression once individuals have initiated on ART (OGAC presentation, 2014).

Conclusion

This study responded to the gaps identified in the scientific literature and provided evidence on the effectiveness of using mHealth interventions to improve post ART retention in care and treatment in a resource limited setting. Reduction of LTF rates has a positive social impact from the individual to the international donor level. In the history of man, no other technology has been accepted and adapted at the level that cell phone use and technology has achieved. Cell phone coverage is available to population in the richest to the lowest resourced countries, and cell phones are in use in the largest cities to the remotest parts of the world. The cell phone coverage continues to increase at a phenomenal rate. Consequently, the acceptability and feasibility of using cell phones in the field of medicine and public health is also continuing to strengthen. This study indicates that mHealth interventions have the capability to reach and lead to behavior change at the individual level, support HIV related public health service goals of individual countries, and provide solutions to meet the global targets set my policy making and funding entities.

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