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INYUVESI YAKWAZULU-NATALI

Long Term Adherence to Antiretroviral Therapy in a South African cohort

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SUPERVISOR DECLARATION

As the candidate's supervisor I, Dr Tanuja N. Gengiah, agree to the submission of this dissertation.

Signed: 

Date: 23 November 2018

DECLARATION

In fulfilment of the requirements of the coursework degree of Masters in Pharmacy in the Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal, Durban, South Africa, I, Atika Moosa, declare as follows:

1. The research reported in this dissertation, except where referenced, is my original work.
2. The work described in this dissertation has not been submitted to UKZN or another tertiary institution for purposes of obtaining an academic qualification, whether by myself or any other party.
3. This dissertation does not contain other persons' text, tables, data, graphs or other information, unless specifically acknowledged as being sourced from other persons.
4. This dissertation does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:

    a. their words have been rewritten but the general information attributed to them has been referenced;

    b. where their exact words have been used, their writing has been placed inside quotations marks, and referenced.

5. My contribution to the project was as follows:

    - Literature Review

    The literature review was conducted using PubMed as the main database to search for published articles. Relevant articles are included in Chapter 1 narrative and key papers are summarized in Table 1 in this dissertation. Review articles were not included in the table but have been referenced in the text.

    - Data Collection, Data cleaning and Analysis

    A full data review and clean up was conducted to ensure that the data analyzed in the manuscript and dissertation was valid and reliable. The data checks, file reviews, corrections and input of missing data were completed by the master's candidate. All required data updates and corrections were checked and verified by the CAPRISA Data Management in accordance with CAPRISA policy on data used for publications. The Masters student completed a quality check of all updates to the database before creating the final data set for analyses. The student conducted some of the statistical analyses, including demographic data analysis and Chi square analysis using SPSS version 25. Results were verified by the CAPRISA statistician using Statistical Analysis System (SAS) version 9.4 software. The

Masters student provided the statistician with the variables to be used in statistical analysis for each study objective.

- Manuscript Write up

The manuscript was written by myself and reviewed by my supervisor before a final draft was submitted to all co-authors for review and comments. Approval for the final version of the manuscript was received from the three co-authors before submission to the journal. The manuscript was submitted to Turnitin to verify for originality on the 30 October 2018.

- Manuscript Submission to Journal

The manuscript was submitted for review and publication to AIDS Patient Care and STDs on 22 November 18

- Write up of Dissertation

I wrote the dissertation before submitting a final draft to my supervisor, Dr Tanuja N. Gengiah, for review and final approval. The final dissertation was submitted to Turnitin on 22 November 18 which was prior to submission to the postgraduate offices.

6. The contributions of others to the project were as follows:
    - Tanuja N. Gengiah – Supervisor and co-author of the manuscript
    - Lara Lewis – Statistician and co-author of the manuscript
    - Kogieleum Naidoo – SAPiT Trial Project Director, TRuTH Study Principal Investigator, Co-author of manuscript
7. Signed: 

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ACRONYMS

3TC	Lamivudine
AACTG	Adult AIDS Clinical Trials Group
AIDS	Acquired Immune Deficiency Syndrome
ALIVE	AIDS Linked to the Intravenous Experience
APROCO	Anti PROtease Cohort
ART	Antiretroviral therapy
ART-CC	Antiretroviral Therapy Cohort Collaboration
ARV	Antiretroviral
ATV	Atazanavir
CAM	Complementary and alternative medicines
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CCMDD	Centralised Chronic Medicine Dispensing and Distribution
CD4	T–lymphocyte cell bearing CD4 receptor
CRF	Case Report Form
CRS	Clinical Research Site
D4T	Stavudine
ddI	Didanosine
DBS	Dried Blood Spot
EC	Enteric coated
EFV	Efavirenz
FDA	Food and Drug Administration
HAND	Human immunodeficiency virus associated neurocognitive disorders
HIV	Human Immunodeficiency Virus
IDU	Injection drug use
IQR	Inter-quartile range
ISAARV	Initiative Sénégalaise d'Accès aux Antirétroviraux
LCMS	Liquid chromatography/tandem mass spectrometry
LPV	Lopinavir
LPV/r	Lopinavir/Ritonavir
MEMS	Medication Event Monitoring System

mL	Millilitre
MMAS	Morisky Medication Adherence Scale
MACS	Multicenter AIDS Cohort Study
MPR	Medication possession ratio
MSM	Men who have sex with men
NRTI	Nucleoside reverse-transcriptase inhibitor
NNRTI	Non-nucleoside reverse-transcriptase inhibitor
NVP	Nevirapine
PCZCDC	Prince Cyril Zulu Communicable Diseases Centre
PEPFAR	President's Emergency Plan for AIDS Relief
PI	Protease Inhibitor
PID	Patient Identification Number
PLWH	People living with HIV and AIDS
QC	Quality control
RNA	Ribonucleic acid
SAPiT	Starting Antiretroviral Therapy at Three Points in Tuberculosis
SHSC	Swiss HIV Cohort Study
SD	Standard deviation
SSA	Sub-Saharan Africa
STI	Sexually transmitted infection
TB	Tuberculosis
TCAM	Traditional, complementary and alternative medicines
TDM	Therapeutic drug monitoring
TRuTH	TB Recurrence upon Treatment with HAART
UKZN	University of Kwazulu-Natal
UTT	Universal test and treat
VACS	Veterans Aging Cohort Study
VAS	Visual Analog Scale
WHIS	Women's Interagency HIV Study
WHO	World Health Organization

ABSTRACT

Background

Current treatment of HIV requires life-long antiretroviral therapy (ART) to suppress HIV replication. Adherence to medication is a critical component of treatment success, where ≥95% of doses, must be taken to achieve and maintain undetectable viral loads which are essential for successful patient and public health outcomes. Although South Africa recently introduced universal test and treat (UTT) and supports the largest number of people living with HIV (PLWH) on treatment in the world, there is limited data on long term adherence in our population.

Objective

The aim of this project was to retrospectively assess long term adherence in HIV infected patients on ART for at least five years or longer in order to inform long term care.

Methodology

Long-term adherence to ART was retrospectively analysed in HIV infected, ART naïve patients, first enrolled in a randomised controlled trial assessing tuberculosis (TB) and HIV treatment integration (N=642) and subsequently followed post-trial in an observational cohort study (N=402) in Durban, South Africa. Adherence was determined by assessing monthly or quarterly (depending on appointment schedule) pharmacy pill counts for patients on ART for five years or longer.

Results

From the initial randomized control trial cohort of 642 patients, 270 met the inclusion criteria for this analysis; 54.8% were female, median age was 34 years (IQR: 29-40) and median time on ART was 70 months (IQR: 64-78). Mean ART adherence was maintained at ≥ 95% for each year on ART and 93.9% of patients maintained viral suppression by the end of the follow up period. Pill count based adherence estimates showed high sensitivity (95%; 95%CI: 91-98%) in predicting viral suppression but poor specificity (9%; 95%CI: 0-41%) for predicting detectable viral loads at five years post-ART initiation. However, half of all patients had at least one sub-optimal (<95%) pill count in the first six months after ART initiation and <20% between the first and sixth year. Viral suppression was 87.4% six months after ART initiation and increased thereafter, remaining >92% throughout follow-up. HIV and TB co-treatment or switching to second line regimens with high pill burdens did not worsen adherence. Mean adherence was >99% in stable patients provided with an extended 90-day ART supply.

Conclusion

Our study found overall high adherence to ART in this South African cohort followed up over a period of more than five years. Treatment outcomes were successful on both first and second line treatment. Pill count was not a good predictor of virologic failure in our study and viral load

measurement should be used as the benchmark for monitoring treatment response as required by current guidelines. However, adherence during the initial six months after ART initiation has been shown to impact long term treatment outcomes, therefore, pill count may be used as a quick, simple measure of adherence to identify patients with early adherence challenges and provide the opportunity for timeous adherence interventions. Optimal long-term adherence with successful treatment outcomes are possible within a structured ART programme with close adherence monitoring. This adherence support approach and these findings are relevant in the era of UTT.

STRUCTURE OF DISSERTATION

This dissertation was written in accordance with the Guidelines for Presentation of Masters Dissertations provided by the College of Health Sciences, University of Kwa-Zulu-Natal, 2015. There is a single reference list using Vancouver reference style for citations in chapters 1, 2 and 4.

The dissertation comprises of the following chapters:

Chapter 1: Introduction – this chapter presents the background on the current HIV epidemic focusing on the key role of adherence on HIV treatment outcomes. The literature review provides a comprehensive overview on methods of measuring ART adherence, factors that impact medication adherence and studies on long-term ART adherence. Current knowledge gaps are identified and provide a prelude to the problem statement and rationale for the study. The research questions raised, and aims and objectives through which these will be addressed, are also described here.

Chapter 2: Methods – this chapter details the study setting, selection of the study population from the SAPiT and TRuTH parent studies, data collection, validation and clean up procedures and methodology for secondary analysis

Chapter 3 - Manuscript titled 'Long Term Adherence to Antiretroviral Therapy in a South African Adult Patient cohort' submitted for publication to the journal AIDS Patient Care and STDs. It is presented in the required format of the journal and is the final submitted version approved by all co-authors. The objectives and aims of the study were addressed in this manuscript.

Chapter 4: Discussion – this chapter is an overall discussion of the study findings and places them in context with findings from other long-term adherence studies. Recommendations for clinical practice, the role of the pharmacist in monitoring and supporting adherence in patients on lifelong ART and possibilities for future research are also discussed.

CHAPTER ONE: INTRODUCTION

CHAPTER 1: INTRODUCTION

1.1 Background and the context for the study

More than three decades have passed since the human immune deficiency virus (HIV) was discovered in 1983 (1). Since the start of the epidemic, HIV has infected 70 million people and claimed the lives of approximately 35 million people globally (2). Currently, an estimated 36.9 million people are living with HIV (PLWH) worldwide (3). Sub-Saharan Africa (SSA), where an estimated 3200 new infections occur daily, bears the highest HIV infection burden globally (2, 3). In this region, South Africa is the country with the highest adult HIV prevalence (18%) and has approximately 7.5 million PLWH, the largest globally (4, 5).

There is currently no known cure for HIV infection (6, 7). Treatment involves the use of combination antiretroviral (ARV) drugs which suppress replication of HIV thereby slowing down disease progression and destruction of CD4 cells that are vital to immune system function (8). Zidovudine was the first ARV drug to be licensed by the United States Food and Drug Administration (FDA) in 1987 and 28 years later we now have six different classes of ARVs comprising more than twenty five individual ARV drugs (9). The advent of antiretroviral therapy (ART) has changed the face of the HIV epidemic by dramatically reducing morbidity and mortality in PLWH. With early initiation of ART, life expectancies for PLWH are now approaching that of the general population (10-12). To lower morbidity and prevent premature mortality ART must be used life-long in order to maintain viral suppression and consequentially HIV is managed as a chronic disease.

In South Africa, the government funded national ARV programme is the largest of its kind in the world providing ARV treatment and care to over four million people (13). In May 2016 the Minister of Health announced that CD4 thresholds would no longer be used as a criterion for ART eligibility and a universal test and treat (UTT) policy was implemented on 01 September of that year (14). This test and treat policy followed updated WHO guidelines from September 2015, based on new evidence, that demonstrated starting ART as soon as possible after HIV diagnosis improves morbidity and mortality outcomes (15, 16). With the implementation of this policy, the number of HIV infected individuals eligible to start antiretroviral treatment is set to escalate substantially. However, increased access to ART is only one aspect of an effective HIV management programme. As treatment programmes scale up our public health facilities face the challenge of rapidly providing pre-ART initiation education and adherence counselling after an HIV infection diagnosis, thereafter, continuing to monitor and provide adherence support and counselling in addition to retaining patients in life time care, all within limited budgets and insufficient human resources (17).

Medication adherence in the context of HIV infection remains critical, as near perfect adherence levels (≥95%) are required to achieve and maintain viral suppression (18). This adherence value was

based on an early study in patients receiving unboosted protease inhibitor (PI) regimens although subsequent studies have reported that viral suppression can be attained at lower adherence levels with non-nucleoside reverse transcriptase inhibitor (NNRTI) and boosted PI regimens (19-21). However, sub-optimal adherence can lead to inadequate concentrations of ARV drugs allowing continued HIV replication and development of drug resistance (22). Indeed, cumulative adherence levels of <100% and treatment interruptions have been found to be associated with an increased risk of treatment failure and resistance to nucleoside reverse transcriptase inhibitor (NRTI) and NNRTIs (23-28). This can have several negative consequences on both individual and public HIV healthcare. Firstly, poorly adherent patients who acquire resistance to first line NNRTI-based regimens are switched to second and third line ARV regimens which are costlier, have a higher pill burden, increased dosing frequency and often have less tolerable side effects (29, 30). Access to second line, third line and salvage treatment regimens are also limited or may be unavailable in resource constrained healthcare settings (31-33). Secondly, resistant HIV strains can be transmitted to others resulting in primary resistance to first line treatment regimens in newly infected ARV-naïve patients or acquired resistance in infected patients already on ART (34). Thirdly, treatment failure due to non-adherence is associated with a greater risk of progression to Acquired Immune Deficiency Syndrome (AIDS) and mortality (35, 36). Hospital admissions due to HIV disease progression and opportunistic infections in poorly adherent patients further add to the burden of public healthcare costs (37-39). Therefore, although NNRTI and boosted PI regimens may be more robust despite imperfect adherence, it is still advocated that high adherence levels be maintained to achieve optimal viral suppression, good treatment outcomes and ensure durability of current available treatment regimens (34, 40).

Adherence to chronic medication is generally not a static phenomenon and patients may alternate between periods of optimal and poor adherence (41-43). Medication adherence rates in chronic non-communicable diseases have been shown to be as low as 50% with discontinuation of therapy usually occurring within six months following treatment initiation (37, 44). Poor adherence levels have also been found in infectious diseases requiring long term therapy such as hepatitis C and tuberculosis (TB) (45, 46).

Studies on short term adherence to ART (from initiation up to two years on treatment) in South African patients have reported adherence rates ranging from 63 to 88% (47-51). However, ART is a chronic, life-long treatment and there is a lack of information on long term adherence in this population. There is a strong emphasis on adherence support and interventions in patients initiating ART but without knowledge on levels of adherence and the facilitators and barriers to adherence over the long term, assisting patients to achieve optimal adherence will remain a challenge. This research aims to address these knowledge gaps by providing insight into long term adherence rates, the factors that influence long term adherence (at least five years or longer) to ART and suggests ways to best monitor adherence in a resource constrained setting.

1.2 Literature Review

Adherence may be broadly defined as "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (44). Patients on ART must take the prescribed number of pills, and doses per day, in addition to following any required dietary and/or fluid restrictions. Studies on ART adherence report optimal adherence to be within the range of ≥ 80-100% of the prescribed doses taken in a specified time period (52, 53). Medication adherence assessed across a spectrum of chronic diseases including hypertension, hypercholesterolaemia and Type II diabetes have been found to be suboptimal with adherence levels reported to be ranging from 37 to 72% (54). Thus, achieving near perfect adherence levels required for successful chronic ART can pose a significant challenge to patients and HIV care providers.

1.2.1 Measures of Adherence

Medication adherence may be measured using indirect and direct methods. Indirect adherence measures include patient self-report, pill counts, prescription refills and electronic monitoring (37, 55, 56). With indirect methods, adherence is generally reported as a rate; usually a percentage of the number of doses taken by the patient over a specified time-period. Direct methods include direct observation of treatment taken, monitoring of drug levels or measuring biomarkers (56). These methods provide objective adherence data however due to higher costs and skilled labour requirements they are rarely used in non-research settings in drugs without a narrow therapeutic range (37). Direct adherence measures are usually report adherence as a dichotomous variable, either adherent or non-adherent, depending on the detection of drug concentrations in plasma, peripheral compartments, or by other biomarkers (57).

Indirect adherence measures

Self-report of medication use is a widely utilised, simple, cost-effective adherence measure where the patient is asked to recall the number of doses taken or missed over a specific period of time before their clinic visit (58). Periods of recall vary widely between studies and range from a few days up to a three months prior to the visit (59). Adherence may be assessed in the form of an unstructured interview, structured questionnaire, such as the commonly used Adult AIDS Clinical Trial Group (AACTG) instrument and Morisky Medication Adherence Scale (MMAS), or a Visual Analogue Scale (VAS) (60-62). The VAS is a linear scale that uses numbers (0-10) or percentages (0-100%) and the patient then selects a point on the line that they think corresponds to their adherence level over the recall period. Self-report is quick and easy to administer but results are prone to bias. Patients may misrepresent their adherence for various reasons; fear of criticism, desire to portray good adherence to care providers, to avoid being probed on reasons for missed doses or be truthfully unable to recall missed doses, leading to an overestimation of adherence. (63, 64). Self-reported non-adherence, on

the other hand, has been shown to be a more reliable indicator of viral suppression and clinical outcomes (64, 65).

Adherence values may also change depending on the type of self-report method used and the recall time period over which adherence is assessed (66, 67). For example, Gao et al. (66) compared self-report adherence values obtained from a Morisky-type questionnaire, a 2-day recall period and a 2-week recall period. Only 29 % of patients were classified as highly adherent using the Morisky scale whereas 93% and 96% were highly adherent using the 2-day and 2-week self-report. Although various self-report adherence assessment tools have been developed, there is a lack of consensus on the selection of a validated, reliable and standardized self-report measure (58, 59). Strategies to improve the reliability of self-report include; using a validated self-report adherence tool for the sample population, reducing possible report bias by using written or computer assisted surveys rather than face-to-face questionnaires, selecting self-report measures that target the adherence behaviour under investigation and having different clinic staff conduct adherence assessments from those who provide adherence counselling and support to minimize social desirability bias (68).

Pill counts, and pharmacy prescription refills are quick and inexpensive methods for measuring adherence making them suitable for use in resource limited settings. Pill count adherence is generally calculated as a percentage using the formula below (69):

$$\frac{\textit{(number of doses dispensed - number of doses remaining)}}{\textit{(prescribed number of doses per day} \times \textit{number of days between the visits)}} \; x\,100$$

Prescription refill data is also used to monitor adherence by utilizing available information from pharmacy dispensing records. However, treatment has to be collected from a single pharmacy or a pharmacy within a linked network in order to be able to monitor adherence (37). Adherence from pharmacy refill records is determined by calculating the Medication Possession Ratio (MPR) or Drug Possession Ratio (DPR) from the following formulae (70-72).

$$MPR = \frac{\textit{total number of days supplied with drug in a time period}}{\textit{number of days from first to last refill in the time period}}$$

$$DPR = \frac{\textit{days' supply of drugs delivered - the days' supply of drugs returned}}{\textit{number of days between clinic visits}}$$

Although not affected by reporting bias these methods may be subject to inaccurate estimations of adherence. Pill counts and prescription refills do not provide information on dose timing and there is no way of determining if the medication is being taken as prescribed. Pill counts can't be accurately calculated if tablets are lost or not brought back by the patient. Pill dumping, where patients return the expected number of tablets and discard the remainder, also presents a false picture of true adherence (37, 73). These obstacles can be avoided by conducting unannounced pill counts, where an unscheduled pill count is done outside the health facility (at the patient's home). Adherence assessed

using unannounced pill counts has been shown to correspond with viral load counts, however, they are costly and time consuming to conduct and are therefore not feasible for routine use in public health care settings (74). Other studies have reported adherence measured using unannounced pill counts, VAS and electronic monitoring were comparable and similarly correlated to viral load suppression (75, 76). Prescription refill data can underestimate adherence if the patient has extra doses that were taken and can overestimate adherence if the patient collects a refill early. Despite their limitations these pharmacy adherence measures have been shown to be superior to self-reported adherence and can assist in predicting virologic outcomes in HIV patients on ART (77-79).

Electronic monitors are a more recent technology gaining popularity in trial settings however they are costly devices for treatment scale up. The most common type is a Memory Event Monitoring System (MEMS) cap which is fitted onto the medication bottle. A data chip in the device records the date and time the medication bottle is opened to remove a dose (80). Objective data can be obtained on dose frequency and time, and data can be captured over extended periods of time. However, opening the cap or removing the dose of medication from the bottle is not a guarantee that it was taken and patients may also remove more than one dose from the bottle at a time which can lead to inaccurate adherence data (37). A review of studies comparing MEMS to other adherence measures found that electronic monitoring systems provided a more accurate adherence assessment than self-report and pill count, which overestimated adherence by 17% and 8% respectively (80). However, a review of studies comparing MEMS and self-reported adherence only found two-thirds of studies demonstrated moderate (27.9%), high (11.6%) or significant (23.3%) correlation between these the two adherence measures (81).

Routine viral load testing (at six months after ART initiation and thereafter annually) is the recommended standard for monitoring patient response to ART, with an undetectable plasma viral load (<50 copies/mL), used as a proxy for adherence to treatment (82, 83). Although viral load measurement is the current benchmark for ART monitoring it is not without limitations. Studies have shown that patients can still have an undetectable viral load despite imperfect adherence, and these patients are at risk of ongoing low level viral replication in non-plasma compartments (84, 85). Virologically suppressed patients with suboptimal adherence were found to have a 50% increased risk of subsequent viral load rebound (86). Annual testing can allow for patient non-adherence to go undetected for up to a year until the next viral load measurement becomes detectable, thereby increasing the risk of treatment failure. It is also not possible to differentiate whether a detectable viral load is due to non-adherence or other causes such as drug resistance or suboptimal drug levels (secondary to drug interactions, malabsorption or other patient factors). Furthermore, due to the infrastructure and skilled labour costs involved, routine viral load monitoring may either be unavailable or have limited accessibility in low income countries (87, 88). There are also operational drawbacks; viral load results are not immediately available, clinics may lack or have inadequate

systems in place to receive and follow up on viral load results; patients with a detectable viral load result may be uncontactable; and patients successfully contacted then have to make a return visit to the clinic for further follow up (89). Point of care viral load testing may circumvent many of these operational challenges as it can be more cost-effective for scale up and provide same day results but there is insufficient evidence available at this stage to recommend wide scale use in public health care settings (90, 91).

Direct adherence measures

Measurement of ARV plasma or urine drug concentrations are not routinely used for adherence monitoring. Apart from the high cost and non-availability in many resource limited settings, therapeutic drug monitoring (TDM) has not been found to provide additional benefit over other routine adherence measures such as self-report and pill count (57, 67). Patients undergoing drug level monitoring may also only adhere to medications immediately prior to clinic visits (92). Using TDM to monitor ARV drug levels can be useful in patients at risk of drug-drug interactions between ARVs and other concomitant medication and those susceptible to altered drug metabolism due to age, physiological abnormalities or co-morbid conditions (93, 94). Dried blood spots (DBS) is a newer method being used to measure ARV blood concentrations and are simpler to collect than traditional venous phlebotomy blood samples (95). A few blood drops from a finger prick are collected on a special filter paper and allowed to dry. The DBS is then placed in a sealed plastic bag with a desiccant and sent to a laboratory for analysis (96). The DBS method does not provide a continuous measure of adherence over time but instead whether detectable concentrations of the ARV drug are present above a certain threshold at the time the DPS sample is taken (97). Viral load monitoring and resistance testing are also possible with DBS making it possible to compare ARV concentrations with virologic outcomes (96). A study in HIV infected pregnant women on ART found DBS to be more accurate than self-report at assessing adherence, with 89% of women reporting perfect adherence by self-report versus 74% adherence determined by ARV concentration in DBS (97). In a West African study, therapeutic concentrations of efavirenz (EFV) and nevirapine (NVP) from DBS where found to correlate with viral load suppression (98).

Measuring the concentration of ARV drug in hair is another novel bio-sampling method being used to determine cumulative adherence to ART (99). A small sample of hair, around 10 to 20 strands, proximal to the scalp is cut from the occipital section of the head (100). Antiretroviral drug levels in the hair are determined using liquid chromatography/tandem mass spectrometry (LCMS) (101). Unlike traditional TDM that measure drug concentrations at a point in time, drugs levels detected in hair samples can be indicative of adherence over a period of weeks to months thereby providing a longitudinal picture of adherence (102). Baxi et al. (103) demonstrated hair concentrations of NVP were predictive of viral load suppression and patients with hair concentrations in the highest quintile

were nine times more likely to have viral suppression compared to patients with concentrations in the lowest quintile. Similarly, atazanavir (ATV) hair concentrations have also been shown to predict viral load outcomes with increasing drug concentrations in hair corresponding to better odds of an undetectable viral load (100). In a study conducted in pregnant women, EFV and Lopinavir (LPV) hair concentrations measured pre- and post-partum were the strongest predictor of viral load suppression at the time of delivery (104). Compared to traditional TDM methods, hair sampling is non-invasive, does not require skilled staff for sample collection and is less expensive. In settings with poor access to viral load monitoring, ARV hair levels could be an alternative method for monitoring adherence.

Ingestible biosensor systems are the latest advance in the field of adherence monitoring (105). The system consists of an oral 'digital pill', a signal receiver and a cloud or web-based server. The drug is embedded with a biosensor during manufacture or co-encapsulated within a gelatine capsule containing the biosensor at the time of dispensing. The embedded or encapsulated drug is ingested and after dissolution in the stomach the biosensor emits a unique signal on contact with gastric fluids, between 30 minutes to 2 hours post-ingestion. The signal is transmitted to a small external receiver worn by the patient. Receivers can be enclosed within a skin patch, mounted on a hip belt or worn around the neck. The data from the receiver, which provides information on the drug name, dosage, date and time of medication ingestion, is then transmitted to a cloud or web-based server. The information can be retrieved on a computer or mobile device using a smartphone application or short message system (SMS) and is accessible to both the patient and health care provider. The undigestible sensor is excreted in the faeces after passage through the gastrointestinal tract (105, 106). The use of ingestible biosensors for ART adherence monitoring is being investigated (107). There are several drawbacks to the system; the sensor or receiver can fail and no data is transmitted even though the medication dose has been taken, patients may find the extent of continuous monitoring intrusive and technology requirements and costs may not make its use unfeasible in real world resource limited settings. The first FDA approved digital medicine system, Abilify MyCite, an antipsychotic drug used for the treatment of schizophrenia and bipolar disorder, was launched in November 2017 (108). Importantly, the manufacturers concede that the system is not indicated to improve adherence (109). This highlights the need for further research in determining the role of ingestible digital tracking systems in modifying adherence behaviour.

There is a great degree of heterogeneity amongst adherence studies with respect to patient populations, study design, methods used to measure adherence, time period per adherence assessment, choice of optimal adherence level and duration of follow up. Hence, while general trends may be observed it is difficult to generalize results between studies using different or even the same measure of adherence. Despite the tendency to overestimate adherence, self-report is the most commonly used adherence measure as it can be easily adapted for almost any type of patient setting. In resource

limited settings the combination of self-report with other low cost adherence measures such a pill count or prescription refill can provide a more accurate adherence assessment (110). Pill count and refill data have also been found to be superior to self-report in predicting viral outcomes and treatment failure (57). Although MEMS has the advantage of providing accurate data on daily dosing and dose timing, its high cost makes it unsuitable for use in real world patient settings (69). Developing technologies such as DBS and hair sampling have demonstrated favourable results in predicting adherence when compared to viral load but their application is currently limited to the research setting (99). The aim of ART is to suppress viral replication to undetectable levels in the blood, therefore viral load monitoring is considered the gold standard for monitoring adherence and response to treatment (89). However, viral load measurements do not provide information on adherence behaviour such as missed doses, missed pharmacy refills or reasons for non-adherence. Using viral load in combination with other adherence measures can improve the accuracy of adherence assessments, enable earlier detection of adherence problems and allow for timeous adherence support before viremia occurs (78, 111).

1.2.2 Factors Influencing Adherence to ART

Adherence to ART may be influenced by five aspects; patient factors, treatment regimens, disease factors, socio-economic factors and the health care system (44). These are discussed in further detail below.

- Patient factors

Patient-related variables that may impact on adherence include demographics, culture and belief systems, acceptance of HIV status, psychosocial factors and self-efficacy (confidence in being able to take medication correctly) (112, 113). Although some studies have reported associations between adherence and demographic variables such as age, gender and race others have found no significant relationship between them (113).

Forgetfulness is a common reason for missing ART doses and is one the most frequent patient reported reasons for non-adherence in SSA patients (114, 115). “Simply forgot’’ was given as the reason for missed doses in over 40% of patients in a study by Bhat et al. (116) in rural South Africa. In studies conducted in Nigeria and Kenya, a third of patients reported forgetting doses in the previous week and month respectively (117, 118). Other frequent patient reported reasons for non-adherence include being busy, being away from home and changes in daily routines (119).

In ART adherence studies that report an age-adherence link, older age is usually associated with higher adherence levels. A meta-analysis by Ghidei et al. (120) found a 35% decrease in the risk of non-adherence amongst those aged 45-55 years old. A large United Kingdom cohort study found improved odds of achieving ≥ 95% adherence for every 10-year increase in age (121). Younger age (<30 years) has been associated with poorer adherence in several studies (42, 122-124). In older

patients (≥50 years) on the other hand, adherence may be impaired due to age-associated cognitive impairment but this has not been a consistent finding (125-127). Elderly patients may also have a higher medication burden and experience medication-related adverse effects due to treatment for co-morbid conditions including cardiovascular disease, diabetes and cancer, which can present a barrier to maintaining optimal adherence to ART (128).

Studies in developed countries have reported a lower proportion of women achieve optimal adherence to ART when compared to men (129). Gender differences with respect to ART adherence must be interpreted within the broader context of other psychosocial factors, such as injection drug use (IDU), alcohol use and depression, which are more prevalent amongst women with poor adherence in developed countries (43, 129-131). However, a Canadian study found female gender to be independently associated with poorer long term adherence to ART with 57% of women optimally adherent to ART compared to 77% of men (132). Gender differences in adherence to ART have not been consistently shown in resource limited countries. In a Senegalese cohort, women were 37% more likely to achieve optimal adherence to ART than men (133). However, Boulle et al. (134) reported no association between gender and self-reported adherence in a Cameroon cohort, although men were found to be at greater risk for virological failure. Nevertheless, HIV infected women in developing countries tend to demonstrate better health seeking behaviours than men which may be motivated by their role as the primary care giver in their families (135, 136). Woman access healthcare more frequently through the use of family planning and antenatal clinic services and are thus more likely to access HIV testing and initiate ART than men (137, 138).

Immigrants and minority ethnic groups in developed countries are less likely to achieve optimal ART adherence although socio-economic challenges such as unemployment, immigrant status, insecure housing and cultural and language barriers may be contributing factors toward the poorer adherence observed (139-141).

Alcohol abuse and active substance abuse are well established barriers to ART adherence. Alcohol abuse reduces adherence by as much as 50-60% with increasing amounts of alcohol consumption corresponding to declining adherence levels (142). Illicit drug users have a four times greater risk of poor adherence compared to non-drug users (143). Non-adherence may be to unintentional due to intoxicating effects or intentional due to uninformed concerns about interactions between ARV treatment and alcohol or illicit drugs (142, 144). Although much of the current evidence is based on studies in resource rich settings similar trends, particularly with relation to alcohol, are evident in African countries (145, 146). In recent years, the use of a drug cocktail containing ARV drugs amongst substance abusers has emerged in South Africa. Known colloquially as “Whoonga”, it reportedly contains a mix of illicit drugs with crushed ARV drugs, usually EFV, added in and the concoction is then smoked (147). The presence of ARV drugs in Whoonga does not provide any

therapeutic effect and it is smoked solely to induce an intoxicating effect. Recreational use of ARV medication may impact on adherence through the diversion of medication for Whoonga use through theft of ARVs from HIV patients (147, 148).

Psychological issues such as stress and depression has been found to be a barrier to ART adherence as feelings of hopelessness, difficulty in coping with HIV related issues such as stigma, and the need for life long treatment, can impair motivation to adhere to ART (149-151). A meta-analysis of ART adherence studies in SSA populations found levels of optimal adherence to be 55% lower in depressed patients compared to those without depression (152). Another meta-analysis that compared findings across low and middle income countries reported an overall 42% reduction in the probability of achieving ≥80% adherence levels in depressed patients with no differences in the rates of depression reported between the different income countries (153). However, a significantly higher proportion of depressed patients from low income countries compared to high income countries achieved ≥80% adherence (153).

Fear of stigmatisation can lead to non-adherence as patients may hide medication and miss doses to avoid disclosing their status to a partner or family members. For women; fear of partner violence, accusations of infidelity and withholding of financial support are barriers to disclosing HIV status to their partners (154-156). Strong interpersonal relationships that provide social support and allow safe disclosure of HIV status has been reported to aid adherence (115).

Traditional, complementary and alternative medicines (TCAM) are often used as adjunctive therapy to ART amongst HIV positive patients across high- and low-income regions (157). Reasons for TCAM use include management of ARV side effects, to improve immune function and treat HIV related co-morbid conditions (158, 159). Patients may decide to use complementary and alternative medicines (CAM), such as immune boosters, vitamin or dietary supplements, and stop their ART leading to non-adherence to their treatment. Studies in developed countries have found CAM use did not affect adherence to ART (158, 160). In African countries, studies have shown mixed results with some finding CAM use had no effect on ART adherence and others reporting poorer adherence due to CAM use (159, 161, 162). Despite their widespread use, patients often do not disclose CAM usage to healthcare providers and non-adherence to ART due to concomitant CAM use is unlikely to be discovered (160, 163). Therefore, it is important for health care practitioners to openly discuss TCAM use with patients in order avoid potential adverse effects, drug interactions and poor adherence secondary to TCAM use.

- Socio-economic factors

A review of earlier studies up to 2005 by Falagas et al. (164) reported that socio-economic factors such as income, employment status and education were not a determinant of ART adherence, however, the majority of the studies reviewed at the time were conducted in the USA. A review on the

effect of socio-economic conditions on adherence in middle and low-income countries did not find a definitive association between socio-economic factors and adherence, however, financial difficulties, poverty, lower level of education and unemployment were found to impair adherence (165). For women taking care of children, it has been reported that those caring for two or more children are less likely to maintain optimal adherence to ART and each additional child in the household results in women having a 6% lowers odds of achieving optimal adherence (166).

In a resource limited region such as Africa, where high levels of poverty and unemployment prevail in most countries, low socioeconomic status may have a greater influence on adherence. Unstable housing, lack of food security, migrant work, inability to afford transportation costs to attend clinic visits, payment of clinic fees and low education levels are significant structural barriers to optimal ART adherence (115, 135, 167-169). As a result, patients may struggle to remain in care and continue on ART treatment and are frequently lost to follow up (170).

- Treatment factors

Complex ARV regimens, high pill burden, dosing more than once a day, food restrictions and special drug storage requirements can impair adherence to ART (171-173). The use of fixed-dose ARV combination tablets, enteric coated formulations, selection of drugs that do not require special storage (for example LPV/r tablets that do not require refrigeration) and simplifying ARV regimens to fit in with the patient's routine have been shown to assist in overcoming these adherence barriers (174-177).

Antiretroviral side-effects and toxicity present another challenge to adherence. Transient (nausea, diarrhoea, fatigue, drowsiness) or persistent (neuropsychiatric symptoms, peripheral neuropathy, dyslipidaemia, lipodystrophy) ARV related side effects can cause patients to interrupt or discontinue ART (178-180).

With the phasing out of older ARVs, such as stavudine (D4T), didanosine (ddI) and unboosted PIs, the introduction of newer, more tolerable ARVs and various fixed-dose ARV combinations, treatment regimen factors such as high pill burden, side effects or toxicity has become less of a barrier to adherence over the years (181).

- Disease factors

Disease severity may affect adherence behaviour with asymptomatic HIV infected patients exhibiting lower adherence to treatment than those who are ill or have a history of opportunistic infections (182). This may be of particular relevance to UTT, where asymptomatic patients that feel well are initiated on treatment and may be less motivated to adhere to treatment. The desire to be well again or remain healthy after being ill may influence symptomatic or previously symptomatic patients to maintain good adherence (182).

Human immunodeficiency virus associated neurocognitive disorders has been shown to reduce ART adherence although further research in this area is needed to determine the exact relationship between ART adherence and cognitive impairment (183, 184).

Increased pill burden due to additional treatment prescribed for opportunistic infections, chronic or acute conditions may also have a negative impact on adherence (185). Tuberculosis is the most common HIV-associated opportunistic infection with half of all new infections occurring in PLWH, 87% of whom are on ART (186). Apart from the increased pill burden, ARVs and anti-TB drugs cause similar side-effects, including rash, gastrointestinal side effects and peripheral neuropathy, which may impair patient adherence to ART (187, 188). Finally, as with other chronic conditions, the need to remain on life-long therapy may lead to treatment fatigue resulting in non-adherence and intentional treatment interruptions (189, 190).

- Health care system

The relationship between patient and health care providers may serve as a facilitator or barrier to adherence. Provision of inadequate HIV and ART education, poor counselling skills, lack of adherence support and uncaring health worker attitudes can lead to incorrect use of medication and non-adherence (124). Language barriers can be a problem in developing countries where health care workers are unable to converse in the local language. Patients may not be able to communicate treatment concerns and adherence challenges or understand verbal and written instructions that are not in their first language (135).

Lack of easy access to health care facilities, particularly in rural areas, high patient clinic loads and lengthy waiting times at clinics may indirectly affect adherence to treatment (191). Transportation costs and having to take time off work due to long waiting times at clinics make it difficult for patients to receive regular treatment (169). Charging user fees may cause patients to miss appointments or scheduled drug refills if they have no money (135).

Although shortages and stock outs of medications is a global issue, it is a frequent experience for many patients in developing countries (192-195). Stock outs impact adherence directly as patients are forced to leave the healthcare facility with no medication, an inadequate supply of medication or their treatment regimen must be altered, possibly to a less effective or less tolerable regimen (193, 196, 197). Patients may be unable to afford the cost of repeated clinic visits if a short supply is dispensed and may run out of treatment as a result. In South Africa stock outs are often due to a breakdown in the drug supply chain. A recent survey found that 16 % of facilities in South Africa reported at least one stock out of an ARV or TB medicine over a three month period (198).

1.2.3 Adherence to ART

Antiretroviral therapy became available to patients in developed regions around the mid-eighties and to African patients only in the early 2000's. Access to ART in African countries was made possible by reductions in the cost of drugs and the concerted efforts of donor organisations such as Global Fund and the President's Emergency Plan for AIDS Relief (PEPFAR) (199, 200). In South Africa, efforts to provide treatment to PLWH were delayed, with detrimental consequences, due to AIDS denialism by the government at the time (201). Finally, in late 2003 after intense lobbying by activists, the South African government began a roll out of its first national program providing free access to ART (202).

Concerns were initially expressed about the ability of patients in developing countries to achieve and maintain the high adherence levels required for ART. Poverty, low levels of education and literacy, lack of health care worker skills and poor infrastructure were amongst the issues raised as barriers to successful treatment outcomes and fears of widespread drug resistance were raised (203-205). However, early studies in Africa found patients were able to achieve optimal adherence levels and outcomes were comparable to those in developing countries (50, 75, 206).

Adherence to ART in developed and developing countries

A meta-analysis on ART adherence studies conducted up to April 2006 in North America and Africa reported 55% of North American patients and 77% of African patients attained optimal adherence (52). The authors noted that North American patients had a longer duration of ARV exposure and treatment regimens were more complex which may account for the lower adherence rates observed. In contrast, studies in Africa reflect adherence seen in ART naïve patients recently initiated on ART using standardized regimens (52). While initial high adherence rates in African patients are encouraging, as treatment programmes expand, retaining patients in care and maintaining good adherence levels over the long term may be a challenge (207, 208).

A 2016 review of adherence studies in Latin American and Caribbean patients on ART reported a pooled adherence rate of 70%, similar to adherence levels reported from developed countries (209). Within these regions, adherence rates were better (80%) in the low and low-middle income countries compared to middle income countries (70%) (209). Alcohol abuse, unemployment, depression and substance abuse were reported adherence barriers (209).

Mhaskar et al. (210) conducted the first meta-analysis assessing ART adherence in India and also reported a pooled adherence of 70%, although the quality of evidence from studies was noted to be poor.

Ortego et al. (53) conducted a 2011 meta-analysis on adherence studies from Africa, the Americas, Western Europe and Asia and found only 62% of patients reported adherence levels ≥ 90%. A greater

proportion of patients in developing countries and men who have sex with men (MSM) were found to report ≥ 90% adherence (53).

A cohort study comparing optimal ART adherence (≥ 95%) between patients in Asia and SSA, two regions with high HIV incidence, found Asian patients reported optimal adherence at 95% of visits and SSA patients at 93% of visits (196). Adherence also improved over time with the number of patients reporting <95% adherence reduced by half in the African cohort and by 70% in the Asian cohort over a two year period (196). Within each region, patients from high income countries had better optimal adherence rates than those who lived in middle and low-income countries (196). Determinants of suboptimal adherence in SSA patients included male gender, younger age, concomitant medication and receiving treatment at a public facility and in Asian patients MSM had 0.6 lower odds of sub-optimal adherence compared to heterosexual patients.

Long term ART adherence

A PubMed search was conducted up to the end of June 2018 using the MeSH terms 'antiretroviral therapy, highly active' and 'adherence, medication'. The search was refined to identify long term adherence publications by adding the search terms 'long term' and 'longitudinal' and excluding 'cross-sectional'. Results were restricted to publications in English and studies conducted in ages 19+ years. Studies were included if the reported follow up time (mean or median) was at least 2 years and longer (Table 1).

In the reviewed literature, long term adherence studies conducted in developed countries include a larger proportion of males and key risk populations (e.g. MSM and IDUs) whereas in developing countries, where women bear a disproportionate burden of the HIV epidemic, studies include a higher percentage of women.

In developed countries, long-term adherence to drug therapy for chronic disease conditions has been found to be suboptimal and similar findings have been observed with adherence to ART (44, 54). Knobel et al. (28) investigated long term adherence in a Spanish cohort over a median follow up period of 8.3 years and only 62% of patients had ≥90% adherence at their last year of follow up. Interestingly, in patients on treatment for more than 3 years, a third of those who had been adherent became non-adherent whereas just over 40% of patients initially non-adherent became adherent whilst only one third of patients were able to maintain continuous optimal adherence thus demonstrating the dynamic nature of adherence behaviour (28). A similar trend in declining adherence was reported in a Canadian cohort study where adherence measured by pharmacy refill dropped from 79% at 6 months to 72% at 24-30 months post ART initiation (35). In an Italian cohort, where adherence was assessed using self-report and pharmacy refill, there was a drop in the proportion of patients with ≥90% adherence from 88% six months after ART initiation to just below 80% after 12 months, although the incidence of sub-optimal adherence halved after 24 months which could suggest a possible reduction

in non-adherence rates in patients who have been on long term ART (211). A study incorporating self-reported adherence data from separate MSM and female cohorts over a five year period reported declining adherence amongst white MSM (91% to 80%) whereas adherence rates were stable but lower in black MSM and women at 75% and 77% respectively (43). In women, substance abuse and alcohol use were associated with poor adherence and in men depression and substance abuse predicted lower adherence (43). Puskas et al. (132) investigated the effect of gender on long term adherence and demonstrated significantly lower proportion of women were ≥95% adherent to ART compared to men (57% vs 77%). A study conducted on the large French Anti PROtease Cohort (APROCO) cohort, consisting of over a thousand patients on ART, reported only a quarter of patients maintained optimal adherence based on self-report over a ten year follow up period (212). Being European born, depression, IDU, ARV side effects, PI regimen, once daily and three or more times a day dosage regimens were associated with moderate to low adherence (123).

Several other studies conducted in developed countries have shown an improvement in ART adherence over time. In a United Kingdom study in patients on ART for up to 13 years, the odds of attaining >90% adherence increased 2% for each year on ART and episodes of low adherence (≤60%) declined from earlier (1999) to later years (2008) (121). A study from the Veterans Aging Cohort Study (VACS) in the USA also found a slight improvement in the number of patients with ≥95% adherence, from 37% to 42%, over a ten year study period (72). In an analysis conducted in separate MSM and IDU cohorts, also in the USA, self-reported adherence increased 11% and 14% every two years in each cohort respectively (213). Notably, in both cohorts, alcohol users, and those with active IDU and substance abuse were less likely to report ≥95% adherence (213). Adherence in the Swiss HIV Cohort study (SHCS) also showed improvement over a six year study period with the proportion of patients with 100% self-reported adherence increasing from 70% to 83% by study end, although only approximately half of the cohort reported maintaining 100% adherence throughout the study duration (42). Interestingly, a separate analysis on patients originating from SSA within the SHCS found these patients reported poorer adherence and had an increased risk of virological failure compared to their European-born counterparts (141). Studies in Netherlands also reported SSA patients on ART had lower ARV plasma concentrations and were at greater risk of virological failure compared to indigenous Dutch patients (214, 215). Socioeconomic factors such as immigrant status, unemployment, unstable housing, cultural barriers and lack of support structures may present as adherence barriers in this patient group.

Poor long term adherence in developed countries has been associated with female gender, younger age, belonging to an ethnic or race minority, active substance abuse, alcohol abuse, depression, prior episodes of virological failure, high pill burden, use of unboosted PI inhibitor regimens, dosage frequency of more than twice a day and lack of partner support (43, 121, 132, 211, 212).

There is a paucity of literature on long term adherence in African populations. One cohort in which long term adherence has been extensively investigated is the Senegalese Antiretroviral Access Initiative where patient adherence was assessed by self-report and pill count over 7 years. The proportion of patients with optimal adherence (≥ 95%) declined in the initial four years of follow up but adherence levels stabilised above 71% after the fourth year (216). The overall mean adherence was 91% and three quarter of patients had optimal adherence levels at the end of the study period (216). There was substantial variability in patient level adherence over time with three average adherence patterns characterised: consistently high adherence, declining initial adherence that increased over time, and high initial adherence that declined over time thus demonstrating the changeability in long term adherence behaviour (133, 217). Women were found to have 37% greater chance of achieving ≥95% adherence compared to men, whereas patients on an Indinavir (IDV) based regimen had a 30% lower adherence compared to those on NNTRI based regimens (133).

A large cohort study in Nigeria found that in over 5500 patients on ART for more than five years, more than 80% of patients demonstrated adherence levels ≥95% measured by pharmacy refill (218). Patients who had consistently higher adherence during the first three years after ART initiation were less likely to withdraw from treatment, be lost to follow up or die (218).

Meresse et al. (219) reported that 75% of patients in a multicentre study in Cameroon had ≥80% adherence in the 12-24 month period after ART initiation. This study also demonstrated the shifting nature of adherence behaviour over time as a quarter of patients who had optimal adherence during the first six months after starting treatment had a least one episode of either non-adherence or interruption of treatment in the second year. Eighty percent of patients who were non-adherent or had treatment interruptions in the initial 6 months of treatment became adherent in the maintenance treatment phase. The odds of non-adherence in men was double compared to women, while patients who were non-adherent in the first 6 months after starting ART had a seven times greater risk of virological failure.

Botswana was the first SSA country to provide free public access to ART. Results from a five year follow up of 633 patients initiated on ART in 2002, 60% of whom were female, found a 92% overall mean adherence by pharmacy refill (220). Only a minority of patients, just over 10%, had ever missed two or more refill visits in a year (220). Although not used to assess adherence in this study, pharmacy pill counts were conducted at each visit and patients were counselled accordingly.

El-Khatib et al. (27) reported 94% of patients in a South African cohort, on ART for a median of 3.7 years, had ≥95% adherence determined by pharmacy refill visits. The main patient reported reasons for non-adherence were being away from their home, forgetting and being busy with other responsibilities (27). Patient characteristics, socioeconomic and clinical variables did not impact on

adherence but a significant association was found between cumulative drug refill adherence of <95% and an increased risk of virological failure.

Table 1: Summary of long-tern ART adherence literature

Year/ Country/Study setting	Study Design	Sample size, n	Age, years	Gender, male %	Duration of follow up, years	Adherence Measure	Period of adherence assessment	Optimal Adherence, %	Proportion of cohort with Optimal Adherence	Proportion of cohort virally suppressed
USA & European Studies										
2006, Italy Single centre, hospital clinic (211)	CS	171	41.2*	67.3	3*	SR, PR	SR – 3 month recall, PR – quarterly review	≥90	NR	47%
2006, France multicentre, clinics (123)	CS	1110	37†	78	5	SR	previous 4 days	100	63%	58%
2007, USA Multicentre study (43)	CS	640[a] 1304[b]	44.1*[a] 38.8*[b]	33	5	SR	previous 3 or 4 days	100	77%	NR
2009, Canada Multicentre, health facilities (35)	CS	903	41†	79	2.75†	PR	6 month intervals	≥95	72%	NR
2009, France Multicentre, clinics (212)	CS	1010	38.9*	78.5	10	SR	previous 4 weeks	100	26%	NR
2009, Spain Single centre, hospital clinic (28)	CS	540	36.25†	69	8.3†	SR, PR	SR – previous month; PR – previous two months	>90	62%	59%

Year/ Country/Study setting	Study Design	Sample size, n	Age, years	Gender, male %	Duration of follow up, years	Adherence Measure	Period of adherence assessment	Optimal Adherence, %	Proportion of cohort with Optimal Adherence	Proportion of cohort virally suppressed
2010, United Kingdom Single centre, clinic (121)	CS	2060	41[†]	78	4.5†	PR	6 months	≥95	51%	NR
2010, Switzerland Multicentre, clinics (42)	CS	6709	41[†]	69.6	4.5†	SR	previous 4 weeks	100	83%	NR
2015, USA Multicentre, health facilities (72)	CS	21 865	45.7[*]	98	10	MPR	yearly	≥95	42%	92%
2015, USA Multicentre, health facilities (213)	CS	1006[a] 197[c]	49.2[*a] 49.8[*c]	100[a] 67.8[c]	10	SR	4 days[a] 3 days[c]	≥95	90%[a] 92%[d]	79.9[a] 65.6[c]
2017, Canada Multicentre, health facilities (132)	CS	4534	women:38[†] men:42[†]	80.1	5.5[†]	PR	6 month intervals	≥95	women - 57.0% men –77.1%	NR

Year/ Country/Study setting	Study Design	Sample size, n	Age, years	Gender, female %	Duration of follow up, years	Adherence Measure	Period of adherence assessment	Optimal Adherence, %	Proportion with Optimal Adherence	Proportion of cohort virally suppressed
African Studies										
2007, Senegal Single centre, hospital clinic (216)	CS	158	38[†]	50	6.5*	PC	previous 30 days	≥95	73.7%	NR
2008 Botswana Multicentre, clinics (220)	CS	633	34.8[†]	60	3.5[†]	PR	30 days	>90	73.7%	98.3%
2011, Senegal Single centre, hospital clinic (133)	CS	330	37[†]	56	7.6[†]	PC, SR	previous 30 days	≥95	74.8%	NR
2011, South Africa Single centre, clinic (27)	CS	456	NR	77	3.7[†]	PR	cumulative	≥95	94%	81%
2013, Cameroon Multicentre, hospital clinics (219)	CS	254	37*	70.5	2	SR	previous 4 days & previous 4 weeks	≥80	71.2%	58%
2015, Senegal Single centre, hospital clinic (217)	CS	317	37.5[*]	55	7.7[†]	PC	previous 30 days	>95	69%	NR

CS = cohort study
PC = pill count
SR = self-report
PR = pharmacy refill
NR = not reported
MPR = medication possession ratio
[†] median
**mean*
[a] MACS - Multicenter AIDS Cohort Study
[b]WHIS - Women's Interagency HIV Study
[c] ALIVE AIDS Linked to the Intravenous Experience study

Long term adherence has been assessed over lengthier time periods in USA and European cohorts than in African studies. This is explainable by the fact that ARVs became available in developed countries approximately two decades earlier than in most developing countries, therefore, patients from developed countries have been exposed to ART for longer. The exception is the Senegalese Initiative Sénégalaise d'Accès aux Antirétroviraux (ISAARV) cohort, where patients had access to ART as early as 1998 and duration of follow up is longer (7 years) compared to other African cohorts. However, ART has been available for more than a decade in Africa and there is an evident lack of data on long term adherence in African patients with only six studies identified in the literature review, three of which are from the ISAARV cohort, and only one study in South Africa. There are several well defined observational cohorts of PLWH on ART in developed countries that report on adherence and patient outcomes including SHCS, APROCO, VACS, MACS, WIHS and Antiretroviral Therapy Cohort Collaboration (ART-CC). A similar effort is lacking and much needed in Africa and other developing nations where the burden of HIV is highest.

Patients in USA and European cohorts were treated with early era ART regimens consisting of various unboosted and boosted PI based regimens whereas treatment regimens in African studies are standardized once daily NNRTI-based regimens using either EFV or NVP. Early era ART regimens had a higher pill burden, required more than once daily dosing, were prone to side effects and toxicity, all factors which may impair adherence (178). A number of studies found PI regimens were associated with poorer adherence; Knobel et al. (28) reported a two-fold higher risk of non-adherence for patients on unboosted PI regimens, 40% of patients on unboosted PI regimens had worsening adherence and 38% had poor adherence in the SHCS, and a PI regimen was also associated with suboptimal adherence in the ISAARV, APROCO, MACS and VACS cohorts (42, 43, 72, 212, 216). Moreover, studies have reported that patients initiating ART in later calendar years demonstrated better adherence. For instance, in the SHCS only a third of patients initiating ART in 2003 had perfect adherence but the proportion of adherent patients increased in each subsequent year of ART initiation with 78% of patients initiating ART in 2012 reporting no missed doses (42). Puskas et al. (132) reported patients initiating ART in the 2000-2004 year period were 40% less likely to be adherent compared to patients who started ART in 2008 and after. Similarly, in the VACS cohort there was a 16 % increase in adherence from 2001-2005 to 2006-2011 (72). Phasing out of unboosted PIs, introduction of fixed drug dose combinations and availability of newer, better tolerated ARV drugs, such as integrase inhibitors, may account for improved ART adherence in patients in more recent years. Due to the later introduction of ART in Africa, patients were not exposed to the afore-mentioned adherence barriers associated with early era ART regimens and the use of standardized regimens and fixed drug combinations may have assisted patients to achieve optimal adherence.

Adherence measures selected for assessment in long term adherence studies should ideally be low cost, easy to implement, adaptable to different settings and be able to conduct over long follow up

periods; self-report and pharmacy adherence measures (pill count and pharmacy refill) fulfil these criteria well. Indeed, self-report was the most frequently used adherence measure in USA and European countries followed by pharmacy refill (28, 42, 43, 123, 211-213). Varying time periods were used to assess self-reported adherence from the previous 3-4 days up to 1-3 months. While it may be easier for patients to provide more accurate responses for a shorter recall period, non-adherence before this time period would be missed. Recall periods of up to 4 weeks or longer may be inaccurate if patients are unable to remember adherence information over the past month/s. In African studies, pharmacy adherence measures were mostly used to assess long term adherence (27, 133, 216, 217, 220). Overall, only three studies used a combination of both these measures to calculate adherence (28, 133, 211). As discussed previously, pharmacy refill may underestimate adherence, for example, if patients collect a refill late but have extra pill doses available and can overestimate adherence if a patient collects a refill early. Although viral load is considered the benchmark for adherence monitoring less than half of all the studies reviewed reported viral load outcomes and it was not possible to correlate long term adherence measures in these studies with viral suppression and patient outcomes.

In summary, there is much variability between long term adherence studies with respect to sample populations, cohort sizes, duration of follow up and assessment of adherence. Patients in long term adherence studies in USA and Europe tend to demonstrate lower adherence than their African counterparts. A limitation in many studies is the lack of viral load monitoring making it challenging to determine if the adherence measure used is predictive of virological outcomes. There is a scarcity of literature on long term adherence in Africa and particularly South Africa, which has the largest number of people on ART in the world. This knowledge can assist in identifying patient groups vulnerable to poor adherence and determining where limited resources should be invested in strategies to improve adherence in long term ART care.

1.3 Problem statement and study significance

Near perfect levels of adherence to ART are required to achieve durable viral suppression, prevent drug resistance and improve morbidity and mortality outcomes in PLWH. Early studies in Africa found patients were able to achieve good rates of optimal adherence, however, much of this data is from early treatment programmes that provided access to limited ART regimens. As ART scale up continues and treatment programmes expand it remains unknown whether these early promising adherence rates will be sustained over the long term.

Sub-Saharan Africa has the largest number of PLWH. ART adherence studies in this region have focused on ART naïve patients initiating treatment, adherence within the first year or two post-initiation or adherence at a single point in time (cross-sectional studies). There is a lack of published

data on long term ART adherence in this region, particularly in South Africa, which has the largest number of people on ART in the world.

The cohort of patients studied were on ART for at least five years or longer. It is postulated that patterns and predictors of adherence assessed over this length of time can provide new insights into adherence behaviours in our population setting and help to inform sustainable and effective adherence interventions.

While adherence support is advocated by local ART guidelines, there is no standardized method of adherence monitoring in the resource limited South African health care setting (83). Although viral load is considered the benchmark for monitoring treatment response it is only measured annually in routine HIV care (83). Thus, patients with poor adherence may be identified at a stage where it could be too late to avoid resistance to first line treatment and treatment failure. Examining the relationship between long term adherence by pill count and viral load may help determine if pill count can be used as a reliable method for adherence monitoring when viral load monitoring is infrequent or expensive. Pill count was selected as the measure of adherence for this study as it was identified as a more objective adherence measure than self-report and is cost-effective in a resource limited setting. In addition, ARV doses lost and reported at home are also taken into consideration to provide a more accurate adherence assessment which is not possible with pharmacy refill adherence assessments.

Providing patients with more than one month supply of ART at a time can ease clinic loads and waiting times at public health facilities and save patients time and money spent on monthly clinic visits to collect ART. Understanding adherence in patients who received an extended three month supply of ARV medication may provide evidence to support provision of more than a month's supply of treatment at a time to the benefit of patients and the overburdened health care system.

TB is the most common opportunistic infection in PLWH in South Africa. High pill burden and overlapping side effects (rash, gastrointestinal side effects, hepatotoxicity and peripheral neuropathy) associated with concomitant HIV and TB treatment may hinder adherence to ARV medication. We investigated if there were any changes in ART adherence in patients with recurrent TB during HIV and TB co-treatment.

1.4 Research Questions

- Are there identifiable patterns or trends in long term ART adherence in adult patients ≥18 years?
- What patient factors are associated with optimal (≥95%) and sub-optimal (<95%) adherence in HIV positive adults on long term ART (≥5 years)?
- What is the relationship between pharmacy pill count and viral load in HIV positive adults on long-term ART (≥5years)?

1.5 Aim and Objectives

1.5.1 Aims

The aim of this project was to retrospectively assess long term adherence in HIV infected patients on ART in order to inform long term care.

1.5.2 Objectives

The aim of the study was achieved through the objectives listed below.

I. Assess and compare adherence by pill count and viral load data.
II. Determine if baseline patient and socio-demographic variables predict long term adherence behaviour.
III. Determine the effect of ARV regimen change on adherence by assessing pill count and viral load data six months before and after switch to a second line treatment regimen.
IV. Assess ART adherence during episode/s of recurrent TB treatment by pill count and viral load data.
V. Determine if there are differences in adherence by pill count between patients receiving a monthly versus three monthly ART supply.

1.6 Conceptual Framework

There are 5 key factors that can influence medication adherence – patient factors, treatment factors, disease factors, socioeconomic conditions and health care systems (Figure 1) (44). In the literature review all five groups were identified as determinants of ART adherence.

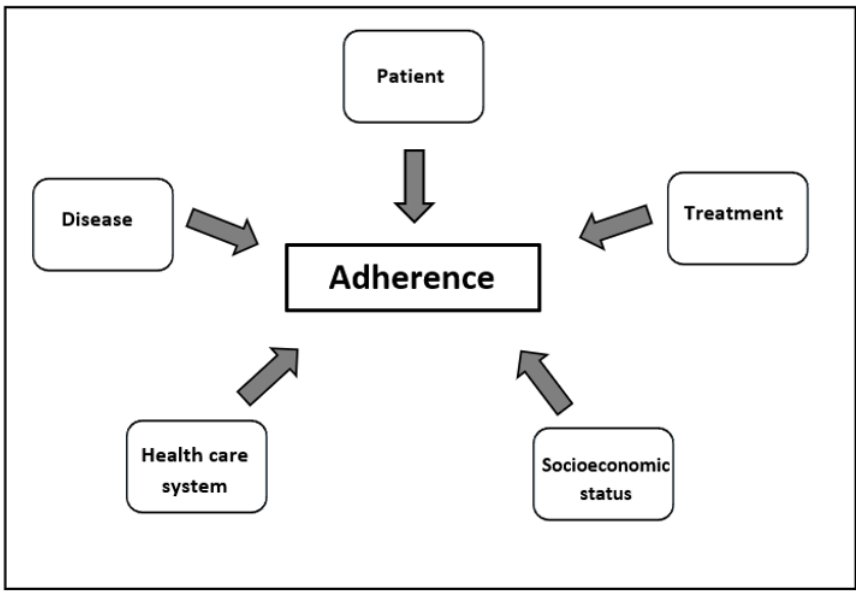

Figure 1: Factors influencing ART adherence

- Patient factors

Demographic variables such as age, gender and race have shown inconsistent results in relation to adherence although age and gender do appear to play an influential role in some settings, with female gender and younger age associated with poor adherence (113, 120, 129, 135, 136). Alcohol abuse, current substance abuse and depression are important barriers to adherence (142, 149). Non-disclosure of HIV status, lack of social support structures and stigma also have associations with adherence challenges (154, 156). Patient related adherence barriers may the most modifiable and much focus is centered on these issues in interventions to improve adherence.

Patient variables that were investigated in this research analysis included age, gender, marital status, number of children, and HIV disclosure.

- Socio-economic factors

Level of education, employment, living conditions and poverty have been reported to affect adherence although less so in developed countries. The effect of poor socioeconomic status on adherence is more evident in resource limited settings where food insecurity, unstable housing, unemployment and financial constraints present significant barriers to adherence (135, 167-169).

Socio-economic variables that were investigated in this research analysis include: employment, education, living conditions and household status.

- Treatment factors

Adherence to a stringent dosing schedule and dietary restrictions together with complex regimens and a high pill burden are a challenge for many patients (37, 171, 172). Side effects, particularly those that cause changes in appearance (lipodystrophy) or affect daily quality of life (neuropathy) further impact on adherence (44, 178, 179).

Treatment related variables that were investigated in this research analysis include ART regimen and pill burden.

- Disease factors

Adherence to therapy for chronic conditions had been shown to be as low as 50% and HIV is no exception despite the more immediate threat of morbidity and mortality(44). The need for life-long therapy can lead to treatment fatigue and non-adherence (189, 190). In asymptomatic patients motivation to adhere may be reduced (182). The presence of co-morbid conditions or opportunistic infections can increase pill burden and impair adherence to ART.

Disease factors that were investigated in the study are the effect of concurrent ART and TB treatment on ART adherence in HIV and TB co-infected patients.

- Health care system

The nature of the patient-provider relationship, access to treatment facilities, user costs for health care services, availability of trained health care personnel and quality of service provided have been shown to influence adherence (124, 135, 198). A breakdown in any of the aforementioned health system factors may negatively affect patient adherence whereas as a well-functioning healthcare system can assist patients to improve and maintain treatment adherence.

We did not investigate the relationship between adherence and the health care system in this study.

CHAPTER TWO: METHODS

CHAPTER 2: METHODS

2.1 Study Design

2.1.1 Setting

This was a retrospective cohort study assessing long-term ART adherence in patients who were initially enrolled in a randomised controlled trial studying TB and HIV treatment integration and subsequently followed up in an observational cohort study on TB recurrence. Both studies were conducted by the Centre for the AIDS Programme of Research in South Africa (CAPRISA) at the CAPRISA eThekwini Clinical Research Site (CRS) located in Berea, Durban, Kwa-Zulu Natal, South Africa. The Kwa-Zulu Natal province has the highest HIV prevalence (16.9%) in the country (4). Within the province, the eThekwini district, which encompasses Durban and surrounding areas, has the second highest HIV prevalence (16.8%) from all metropolitan areas in Kwa-Zulu Natal (221).

Study participants were recruited from the Prince Cyril Zulu Communicable Diseases Centre (PCZCDC) located adjacent to the CAPRISA eThekwini CRS. The PCZCDC is one of the largest public health TB and sexually transmitted infection (STI) clinics in the province, situated near the major transport hub in the Warwick Triangle area and is accessed by thousands of patients from across the larger Durban area.

Antiretroviral treatment was provided to study participants through the CAPRISA AIDS Treatment programme funded by PEPFAR. Access to ART from public health facilities in South Africa was limited at the time.

2.1.2 Sample population

The Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPiT) study was an open label randomized control trial that compared three treatment strategies of ART initiation in HIV and TB co-infected patients (N=642) (222). Participants were enrolled between June 2005 and July 2008. The primary objective of the study was to determine the optimal time to start ART in an HIV and TB co-infected patient. The standard duration of treatment for pulmonary TB in the study was six months; a two-month initiation phase followed by a four-month continuation phase. Eligible male and female adults, 18 years and older, were randomly assigned to initiate ART either within one month of starting TB treatment, or within one month of completing the initiation phase of TB treatment, or within one month of completing the continuation phase of TB treatment. Study patients were initiated on a once-daily, weight-based ART regimen containing EFV or NVP plus lamivudine (3TC) and enteric coated ddI.

TB Recurrence upon Treatment with HAART (TRuTH) was a prospective cohort observational study investigating the rate of TB recurrence in HIV infected adult patients who had completed pulmonary TB therapy and were on ART (N=402). This cohort was comprised of participants from the completed

SAPiT study who were then offered enrolment into the TRuTH study (223). Ex-SAPiT study patients were enrolled into the TRuTH observational study from November 2009 to July 2011 and follow up was completed in April 2014.

All patients received three pre-ART education counselling sessions that provided information on HIV disease, an introduction to ART, individual ARVs in the treatment regimen, ARV side effects and the importance of maintaining optimal adherence to treatment. Ongoing general adherence support post-ART initiation was provided by trained counsellors and site pharmacists in both studies. In addition, pharmacists were involved in targeted adherence counselling to patients who were identified with suboptimal adherence by pill count. Pharmacists also provided pillboxes to all patients as an adherence aid. To assist patients in using the pillbox and ensure they understood how to take their daily ART dose, patients were requested to fill the weekly pillbox in the presence of the pharmacist or counsellor at ART initiation or if there was a change to their ART regimen. Additionally, in patients identified with ongoing adherence challenges, the pharmacist would pack and provide pillboxes with a full month supply of ART to facilitate adherence. Patients that missed their scheduled clinic appointment date were telephonically and/or physically tracked. Treatment supporters, where possible, were enlisted to provide additional support for patients identified with adherence challenges.

Inclusion and Exclusion Criteria

Inclusion criteria:

Participants who were enrolled, initiated on ART, completed follow up in the SAPiT trial and then subsequently joined the TRuTH cohort study were selected for inclusion. In addition, participants had to be on ART for at least five years from the time of ART initiation in SAPiT to study exit in TRuTH.

Exclusion criteria:

Participants who were lost to follow up in SAPiT, did not collect their ARV treatment from the research site pharmacy and for whom pill count data was missing for more than 6 consecutive months were excluded.

A biostatistician was consulted to determine the sample of patients from the afore-mentioned studies eligible for inclusion in the retrospective study. The sample size (N=270) was deemed adequate for the proposed statistical analysis (refer section 2.4)

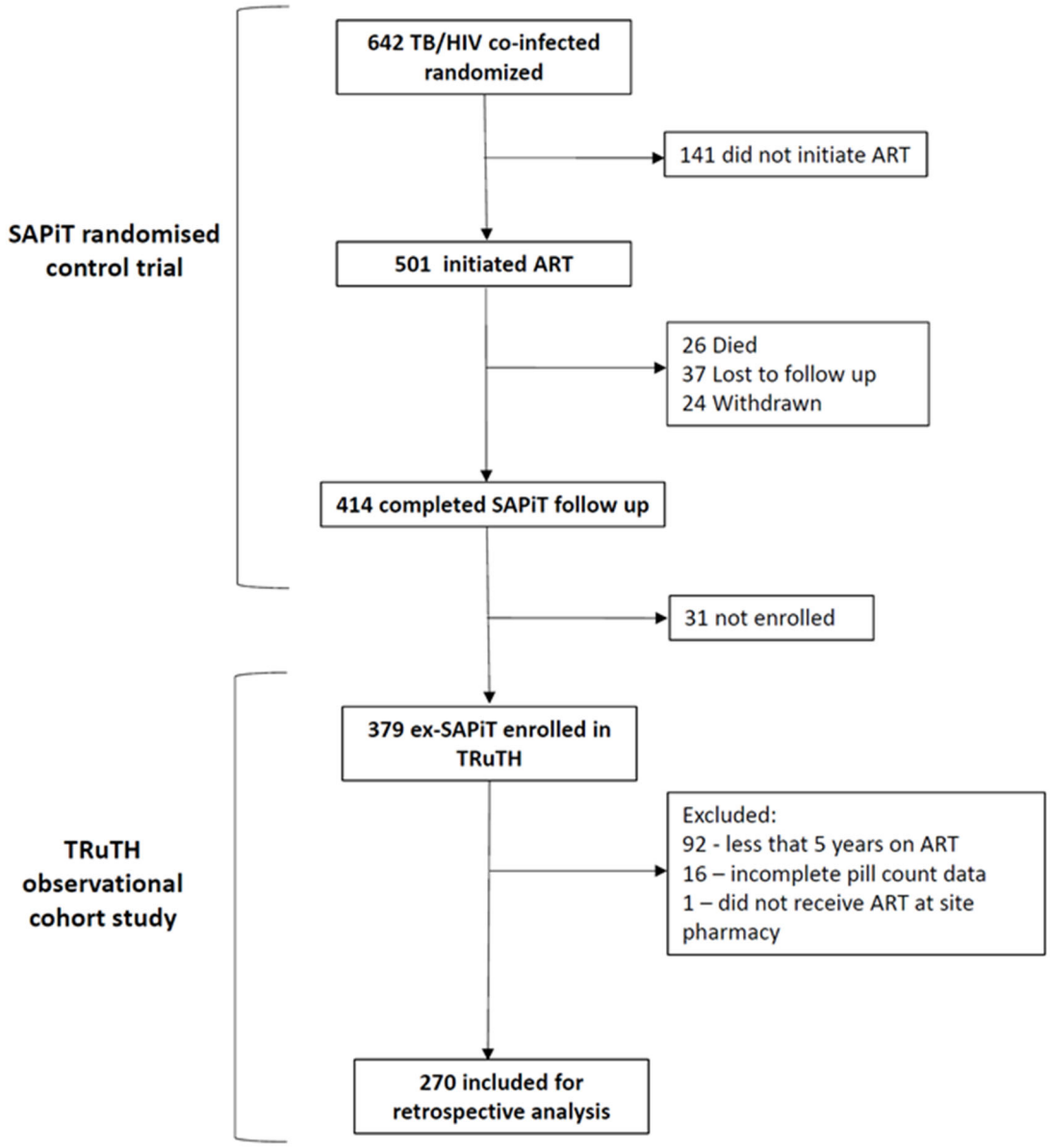

Figure 2: Selection of patient cohort on ART for at least 5 years

2.2 Data Collection

In both the above-mentioned studies validated paper case report forms (CRFs) were used for recording participant-specific quantitative data at each study visit. The CRFs provided a standardised tool for recording information thereby improving data reliability. On enrolment into each study, participants were assigned a unique patient identification number (PID) provided by the study Data Management Centre. This PID was used to identify the participant on each CRF completed at every study visit for the duration of the study. The paper CRF's were filed together with other study documents including clinical chart notes, laboratory results and prescription cards in participant-specific study files stored at the research site.

To ensure content and construct validity, the CRFs were created, revised and updated by the CAPRISA Data Management centre in consultation with the protocol team, including the study pharmacist. The CRF content and questions were dependant on the type of information required to be recorded.

Further measures to improve data validity and reliability included the use of validated equipment for viral load and CD4 measurements, training of study staff on the correct procedures for CRF completion, CRFs were checked for completeness by a member of the Data Management team before uploading to the CAPRISA electronic database and quality control (QC) reports were generated once the data was uploaded. Any incorrect or invalid data entries identified on a QC report were corrected and resolved on the original CRF and re-captured on the electronic database.

Baseline demographics and behaviour variables captured at the SAPiT study enrolment visit included age, gender, household status, marital status, occupation, education, number of children, basic living conditions, HIV testing and disclosure. At ART initiation, the prescribed drug regimen, dosage and treatment start date was captured. Any changes in ARV treatment were similarly documented. Pill count data, which included quantity dispensed and returned, was captured at each scheduled and unscheduled study visit were ARV treatment was dispensed in both the SAPiT and TRuTH studies.

In the SAPiT trial, viral load (Cobas® Amplicor HIV-1 Monitor, version 1.5, Roche) and CD4+ cell count (FACSCalibur™, Becton Dickinson) measurements were performed at the time of screening, at randomization, and thereafter 6 monthly. Viral load (Cobas® Ampliprep-Roche TaqMan®) and CD4+ cell count measurements (Becton Dickinson FacsCalibur™) were performed at least 6 monthly in the TRuTH study. Additional viral load testing would have been conducted if requested by the study clinician. Viral load measurements were recorded on appropriate CRFs.

Adherence to ART during recurrent TB episodes in the TRuTH study were determined by using documented TB treatment start and stop dates.

Table 2: SAPiT CRF Data

Plate #	Data Captured	Variables	Appendix
001 002	Demographics	Age, Gender, Household status, Primary breadwinner, Marital status, Occupation, Education, No. of children, Living conditions	D
003	Baseline Behaviour Questionnaire	HIV testing, HIV disclosure	E
018	HIV Bloods	Viral load and CD4+ cell counts	F
020	ARV Treatment	ARV drug, dosage, duration of use	G

Plate #	Data Captured	Variables	Appendix
024 063	Pill Count	Number of tablets lost, remaining, returned and dispensed	H
030 031	WHO Staging	WHO Clinical Stage 1,2,3, and 4 disease	I
057	Termination from study	Completion of follow up in study	J

Table 3: TRuTH CRF Data

Plate #	Data Captured	Variables	Appendix
018	HIV Bloods	Viral load counts	K
055	TB Treatment	Date of TB treatment initiation and completion	L
063	Pill Count	Number of tablets lost, remaining, returned and dispensed	M
057	Termination from study	Completion of follow up in study	N

2.3 Data Management

Data captured in both studies was stored in a secure electronic database. CRFs selected for analysis where based on data relevant to the aim and objectives of the study. The required variables were downloaded and provided by the data manager (Table 1 and 2). In the event of incorrect, incomplete or missing data being identified, a file review was done to locate the original paper CRF for verification. Corrections made to a CRF were checked by the data manager before the CRF was re-entered into the database with the updated information. Where CRF data was unavailable, other source documentation (chart notes, laboratory results, prescriptions) were reviewed to obtain the required information. The data checks, file reviews, CRF corrections and final data set for analyses were completed by the Masters candidate.

2.4 Data Analysis

Baseline demographic data were obtained on enrolment into the SAPiT trial and were analysed by descriptive statistical methods. Continuous variables are reported as mean with standard deviation (SD) or median with inter-quartile range (IQR). Categorical variables were reported as percentages or frequencies.

Table 4: Variables for analysis

Variable	**Type of variable**	**Descriptive Measure**
Age Viral load CD4	Continuous	median, IQR
Gender Education Household status Primary breadwinner Marital status Occupation Living conditions Number in household HIV disclosure WHO Staging	Categorical (Nominal)	Number, Percentage
Adherence (pill count)	Continuous	Mean, SD

Undetectable viral load was defined as <400 copies/mL. In the SAPiT trial, treatment failure was defined as two HIV-1 RNA measurements of >1000 copies/mL taken at least 4 weeks apart followed by ART discontinuation and switching to a second-line ART regimen consisting of a boosted PI plus two NNRTIs. In the TRuTH study treatment failure was defined as two consecutive HIV-1 RNA measurements of >1000 copies/mL at least six months apart followed by a switch to a second line regimen consisting of a boosted PI plus two NNRTIs.

Adherence to ARV treatment in both studies were determined by pharmacy pill counts. This was assessed at least monthly in the SAPiT trial and either monthly or up to three monthly in the TRuTH study depending on the quantity of ART dispensed. Optimal adherence was defined as ≥95% of doses taken and poor adherence as <95% of doses taken in the specified time period. Adherence percentage was calculated using the following formula:

$$\frac{\text{No. of tablets dispensed at previous visit – Number of tablets returned/ reported remaining/lost at current visit}}{\text{Number of tablets that should have been ingested between visits (daily tablet dose x no. of days between visits)}} \times 100$$

Adherence values were not calculated for visits where a clinician-initiated treatment interruption had been instituted or pill count data was missing e.g. tablets not returned and reported remaining or lost was unknown.

Mean pill count adherence for a given period was calculated as the weighted mean of the monthly and/or three monthly adherence values from the period, where the weights were calculated as the length of time between each visit (i.e. one month or three months). Chi-square tests (α =0.05) were used to determine the association between patient baseline characteristics and optimal adherence over the study period. Sensitivity and specificity values (and associated 95% confidence intervals) were calculated for each year on ART to assess the extent to which mean pill count adherence over the year could be used to identify patients who were virally suppressed by year end. The Wilcoxon signed rank test (α =0.05) was applied to the adherence values and viral load before and after switch to a second line regimen in patients with treatment failure as well as to adherence values and viral load before and after the start of TB treatment following TB recurrence. A Kaplan Meier survival analysis was used to estimate time to treatment failure.

Statistical Analysis System (SAS) version 9.4 software was used to conduct statistical analysis.

2.5 Ethical considerations

The completed SAPiT and TRuTH studies were approved and conducted under the oversight of the Biomedical Research Ethics Committee at the University of KwaZulu-Natal [SAPiT (E107/05) and TRuTH (BF051/09)]. Participants in both studies provided written informed consent. Informed consent forms for both studies described the purpose of the study, study procedures to be conducted at each study visit, and the risks and benefits of study participation. The informed consent forms were also available in isiZulu for participants whose first language was isiZulu. Study participants were reimbursed a nominal amount for each study visit for time spent at the clinic. To ensure confidentiality all participant data has been anonymised by the removal of personal identifiers.

In this retrospective study of SAPiT and TRuTH data, there was no direct participant contact and informed consent was not required as it had been provided when participants joined the SAPiT and TRuTH studies. Ethics Approval for this retrospective study was received from the Biomedical Research Ethics Committee at University of KwaZulu-Natal (BE046/16).

CHAPTER THREE: MANUSCRIPT

CHAPTER 3: MANUSCRIPT

3.1 Manuscript

Long-Term Adherence to Antiretroviral Therapy in a South African Adult Patient cohort

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Key words: adherence; HIV; Antiretroviral therapy; pill count; South Africa

ABSTRACT

South Africa supports the largest antiretroviral therapy (ART) programme globally and recently introduced universal test and treat (UTT). Maintaining optimal ART adherence (≥ 95%) is essential for successful patient and public health outcomes. Long-term adherence to ART (≥5 years) was retrospectively analysed in tuberculosis (TB) and HIV co-treated patients in Durban, South Africa. Adherence was comparatively assessed using pill count and viral load data. From an initial cohort of 642 participants, 270 participants were included in the analysis; 54.8% were female, median age was 34 years (IQR:29-40) and median time on ART was 70 months (IQR=64-78). Mean ART adherence was ≥95% for each year on ART and 94% of patients were virologically suppressed at the end of follow-up. Pill count showed high sensitivity (95%; 95%CI:91-98%) in predicting viral suppression but poor specificity (9%; 95%CI:0-41%) for predicting detectable viral loads at 5 years post-ART initiation. However, half of all patients had at least one sub-optimal (<95%) pill count in the first six months after ART initiation and <20% between the first and sixth year. Viral suppression was 87.4% six months after ART initiation and increased thereafter, remaining >92% throughout follow-up. HIV and TB co-treatment, switching to second line ART with higher pill burdens and providing an extended ART supply in clinically stable patients did not impair ART adherence. Optimal long-term adherence with successful treatment outcomes are possible within a structured ART programme with close adherence monitoring. This adherence support approach and these findings are relevant in the era of UTT.

INTRODUCTION

Currently, an estimated 36.7 million people are living with HIV (PLWH) worldwide. [1] Sub-Saharan Africa (SSA) has the largest global HIV burden of infection with prevalence at 4.2% and an estimated 3200 new infections occurring daily. [1, 2] Within this region, South Africa is the country with the highest adult HIV prevalence (18%) and has the largest adult population of PLWH in the world, estimated to comprise approximately 7.5 million people. [3, 4] The country's government funded national antiretroviral (ARV) rollout programme is the largest globally, providing antiretroviral treatment (ART) and care to over four million people. [5] In September 2016, South Africa incorporated the universal test and treat (UTT) policy into its' national ART guidelines. [6] With the implementation of this policy, the number of HIV infected individuals eligible to start ARV treatment has escalated substantially.[7]

Access to ART is only one aspect of an effective HIV management programme. Early studies reported that successful antiretroviral therapy required adherence to daily dosing of ≥95% to achieve and maintain viral suppression. [8, 9] However, more recent studies have shown that virologic suppression may still be achieved with <95% adherence levels but this is dependent on the ART drug combination used, time on ART and previous exposure to ART. [10, 11] Furthermore, repeated adherence levels of <100% and treatment interruptions are associated with an increased risk of nucleoside reverse transcriptase (NRTI) and non-nucleoside reverse transcriptase (NNRTI) resistance which form the backbone of current first line ART regimens in South Africa. [12-14] Thus, although NNRTI and boosted protease inhibitor (PI) regimens may be more robust despite imperfect adherence it is still recommended that ≥95% adherence be maintained to achieve optimal viral suppression and prevent emergence of resistant virus. [15, 16]

Early adherence studies found a comparatively high proportion of African patients were able to achieve optimal adherence to ART.[17-19] In South Africa, short term ART adherence rates (less than two years from treatment initiation) in patients from multiple urban HIV clinics is reported to range from 63 to 88%, however, there is a paucity of information on long-term adherence in this population. [20-23] As treatment programmes continue to expand, and patients become more treatment experienced, determining adherence patterns over the long-term can provide insight into observed treatment outcomes and assist in developing appropriate adherence support and intervention strategies. The aim of this study was to address this knowledge gap by assessing long-term adherence in patients on ART for at least five years in an urban research clinic in Durban, South Africa.

METHODS

Study Design, Setting and Patients

This is a retrospective analysis of long-term ART adherence in HIV infected, ART-naïve patients who were originally enrolled in a randomised controlled trial assessing tuberculosis (TB) and HIV treatment integration and followed up in an observational cohort study assessing TB recurrence at the Centre for the AIDS Programme of Research in South Africa's (CAPRISA) eThekwini Clinical Research site in Durban, South Africa.

Initially, HIV and TB co-infected patients were enrolled in the Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPiT) open label randomised controlled trial from June 2005 to July 2008 (n=642). Details of the study outcomes have been published elsewhere. [24, 25] Study patients were initiated on a once daily, weight-based ART regimen containing efavirenz (EFV) or nevirapine (NVP) plus lamivudine (3TC) and enteric coated didanosine (ddI) either during or after completion of tuberculosis treatment. Viral load (Cobas® Amplicor HIV-1 Monitor, version 1.5, Roche) and CD4+ cell count (FACSCalibur™, Becton Dickinson) measurements were conducted at screening, on randomization into the study and 6 monthly thereafter.

After completion of follow up in the SAPiT trial, patients were offered enrolment into a prospective observational study, TB Recurrence upon Treatment with HAART (TRuTH), to investigate the rate of TB recurrence in HIV infected adults who had completed pulmonary TB treatment and were on ART (n=402). [26, 27] Viral load (Cobas® Ampliprep-Roche TaqMan®) and CD4+ cell count (Becton Dickinson FACSCalibur™) measurements were performed at least 6-monthly in the TRuTH study. Additional viral load testing was conducted if requested by the study clinician. In 2011, ddI was replaced by tenofovir disoproxil fumarate (TDF) in virally suppressed patients in line with WHO recommendations at the time. [28] Ex-SAPiT study patients were enrolled into the TRuTH observational study from November 2009 to July 2011 and follow up was completed in 2014.

Long-Term Adherence

To assess long-term adherence, all patients who were on ART for at least five years from the time of ART initiation in the SAPiT trial until their completion of follow up in the TRuTH study were included in this retrospective analysis. To maintain continuity of care, patients accessed ART after completion of follow up in SAPiT and before enrolment in TRuTH via the CAPRISA AIDS Treatment (CAT) programme at the same clinic. Pill count data was not available for ART that was dispensed in the CAT programme. Patients who never initiated ART, were lost to follow up in the SAPiT trial, did not receive ART from the site's research pharmacy and for whom pill count data was missing for more than 6 consecutive months in either study were excluded from this analysis.

Adherence to ART in both studies were determined by pharmacy pill counts and assessment of viral load data. Pill counts were conducted monthly by the study pharmacist in the SAPiT trial and either monthly or 3-monthly in the TRuTH study depending on the quantity of ART medication dispensed. Optimal adherence was defined as ≥95% of doses taken in the time between the study visits. All patients received pre-ART education and ongoing adherence support counselling by trained counsellors and site pharmacists post-ART initiation. Pillboxes were provided to all patients as an adherence aid. Patients who missed their scheduled clinic appointment date were telephonically or physically contacted. Treatment supporters, where possible, were used as additional support for patients identified with adherence challenges.

Adherence percentage was calculated using the following formula:

$$\frac{\textit{No. of tablets dispensed at previous visit – Number of tablets returned/ reported remaining/lost at current visit}}{\textit{Number of tablets that should have been ingested between visits (daily tablet dose x no. of days between visits)}} \times 100$$

Pill count adherence was not assessed for visits where there was a clinician-initiated treatment interruption or where pill count data was missing.

The parent SAPiT and TRuTH studies were conducted under the oversight of the Biomedical Research Ethics Committee (BREC) at the University of KwaZulu-Natal (BREC ref: E107/05 [SAPiT]; BF051/09 [TRuTH]). The current study is a retrospective secondary analysis of previously collected anonymized data from the parent studies with no direct patient contact (BREC ref: BE046/16).

Statistical Analysis:

Baseline demographic data were obtained on enrolment into the SAPiT trial and were analysed by descriptive statistics. Undetectable viral load was defined as <400 copies/mL. In the SAPiT trial treatment failure was defined as two HIV-1 RNA measurements of >1000 copies/mL taken at least four weeks apart followed by ART discontinuation or change of all drugs in the ARV regimen. In the TRuTH study treatment failure was defined as two consecutive HIV-1 RNA measurement of >1000 copies/mL at least six months apart followed by a change to a second line ART regimen.

Mean pill count based adherence for a given period was calculated as the weighted mean of the monthly and/or 3-monthly adherence values over that time period, where the weights were calculated as the length of time between each visit. Chi-square tests (α =0.05) were used to determine the association between patient baseline characteristics and optimal adherence over the study period. Sensitivity and specificity of the pill count based adherence estimates (and associated 95% confidence intervals) were calculated for each year on ART to assess the extent to which mean pill count adherence over the year could be used to identify patients who were virally suppressed by year end. The Wilcoxon signed rank test was used to analyse the impact of concurrent TB and HIV treatment on

ART adherence in patients presenting with recurrent TB by analysing changes in adherence and viral load suppression before and during TB treatment and was also applied to the adherence estimates and viral load before and after switching to a second line regimen to assess the impact of a change in regimen on adherence (α =0.05). A Kaplan Meier survival analysis was used to estimate time to treatment failure.

Statistical Analysis System (SAS) version 9.4 software was used to conduct statistical analysis.

RESULTS

A total of 270 patients met the inclusion criteria for this analysis (Fig. 1). The median age of the cohort was 34 years (IQR:29-40) and 54.8% were female (see Table 1). At ART initiation the median CD4+ cell count was 145 cells/mm^3 (IQR:76-249) and median viral load was 141 000 copies/mL (IQR:37 757 – 386 000). Most patients (254/270) were classified as WHO stage 3 at baseline. A third of the cohort had completed secondary school, 60% were in full or part-time employment and more than half of all patients had disclosed their HIV status. The median duration on ART from initiation to completion of follow up was 70 months (IQR: 64-78). The time period between patient exit from SAPiT and enrolment in TRuTH (where no pill count data available) was a median of 13 months (IQR: 5-21).

The majority of the cohort (94.8%) had an overall mean ART adherence of ≥95%. Of the 14 patients with sub-optimal adherence, nine had adherence estimates in the 90-95% range, two were in the 80-90% range, two were in the 70-80% range, and only one had less than 70% adherence. There was no statistically significant association between baseline patient demographic or clinical characteristics and optimal adherence to ART (results not shown).

Mean adherence to ART for the entire cohort was ≥95% for each year on ART (see Table 2). In the six months post-ART initiation, 91.8% of patients had optimal adherence. After 6 months, more than 95% of the cohort maintained optimal adherence levels for the remainder of the follow up period. Adherence levels peaked (99.3%) at 18-24 months after ART initiation and remained above 98% from 32 months onward. Half of all patients had at least one sub-optimal adherence measurement (<95%) in the first six months after starting ART, less than 20% between the first and sixth year and 23% after six years on ART. Viral suppression rates were 87.4% six months after ART initiation and thereafter increased and remained above 92% throughout follow up (Fig. 2). Eleven patients had a viral load > 400 copies/mL after five years and 94% of patients were virologically suppressed at the end of the follow up period. Pill count showed high sensitivity in predicting viral suppression but had poor specificity when the viral load was detectable (see Table 3).

Thirty-three patients from the cohort experienced treatment failure, of whom 21 had viral rebound after initially being suppressed on first line ART and the remainder 12 achieved virologic suppression

only after switching to a second line regimen. Approximately half of all treatment failures (n=17) occurred within two years after ART initiation. The cumulative probability of treatment failure was 10.7% at five years after ART initiation (Fig. 3). Adherence and viral load measurements prior to and after switching to a second line boosted LPV/r regimen was available for 22 of the treatment failure patients. The number of patients with optimal adherence improved and there was a significant increase in viral load suppression at 6 and 12 months after being switched to the second line regimen (see Table 4).

In the TRuTH study, patients with optimal adherence by pill count and an undetectable viral load (n=267) were provided with an extended 3-month supply of ART at a total of 1061 study visits. Overall mean adherence for patients who received a 3-month ART supply was 99.5%.

Of the 21 patients diagnosed and initiated on treatment for recurrent tuberculosis in the TRuTH study, three exited the study whilst on TB treatment and one did not complete their course of TB treatment. In the remaining 17 patients, there was a decline in optimal adherence and viral load suppression when patients were on both ART and TB treatment, but this was not statistically significant (see Table 4).

DISCUSSION

Our study found overall high adherence to ART in this South African cohort followed up over a period of more than six years. Treatment outcomes were successful on both first and second line treatment, with 93.9% of patients virologically suppressed at study completion and only 12% experiencing treatment failure over the entire follow up period. Adherence in the first year of treatment was higher (98%) than those reported in several African studies, where adherence estimates ranged from 72 to 94%. [21, 29-33] Intensive pre-ART education and counselling sessions, an ongoing adherence support programme post-ART initiation, provision of pillboxes and use of a once-daily ART regimen, support measures that have been shown to positively influence adherence**,** may have played a role in helping to attain high adherence. [34-37] A previous qualitative study in the SAPiT cohort showed a good patient-healthcare provider relationship, accessible free care and routine remembering techniques played an important role in motivating them to adhere to their treatment. [38] Additionally, enteric coated ddI was used instead of stavudine (D4T) in our first line ART regimen due to its better side-effect profile, thereby avoiding non-adherence and discontinuation associated with stavudine toxicity observed elsewhere. [39, 40]

Adherence was optimal for each year of follow up and remained stable between 98-99% over the six-year period. Long-term adherence studies in Botswana, Senegal and Nigeria also found comparably high adherence levels although in the Senegalese cohort where adherence was assessed over seven years, adherence dropped below 90% during the initial four years before improving and stabilising at 91%. [41-44]

Viral suppression rates exceeded 90% for each year throughout the observation period. Similar long-term virologic outcomes have been reported in other low- and middle-income regions. [40, 45-49] The proportion of patients failing treatment was highest in the two years after ART initiation, thereafter, the number of treatment failures declined with each subsequent year on ART. Non-adherence by pill count was also most frequent in the first six months of ART in our cohort. Poor adherence in the initial months after ART initiation has been shown to increase the risk of virologic failure in later years and these early adherence lapses may be the reason for the higher number of treatment failures initially observed thus highlighting the importance of prioritizing adherence monitoring and support interventions to ensure optimal adherence from ART initiation. [21, 43, 50-52] Studies on long-term virologic outcomes have found the risk of viral failure decreases the longer patients remained suppressed on ART and may account for the declining number of treatment failures observed in our cohort over the years. [53-55]

Sensitivity was high, but specificity was low for the use of pill count data as a proxy for viral load outcomes. Whilst some studies have demonstrated an association between pharmacy adherence measures and virologic outcomes others have found poor agreement between the two measures. [31, 32, 56-59] The use of different optimal adherence thresholds, timing of viral load measurements, definition of viral load suppression and time on ART influence the relationship results between adherence and virologic outcomes. [32, 58] Although we used an adherence threshold of ≥95%, viral suppression has been reported in patients with 85-94% adherence on long-term ART. [60] Furthermore, whilst pill counts provide a more objective method of adherence assessment, patient manipulation is possible as non-adherent patients may discard or leave behind medication not taken and return the desired number of pills to demonstrate good adherence. [61, 62] Even though plasma viral suppression is possible with sub-optimal adherence, low-level viral replication continues in the plasma and reservoirs such as the central nervous system and genital tract, the long-term effects of which have not been fully elucidated. [10, 63] Therefore, high adherence to ART remains essential to ensuring the best clinical outcomes.

Patients who were stable on ART, virally suppressed and had optimal (≥95%) adherence, were sometimes provided with a 3-month ART supply in the TRuTH study. A high mean adherence was maintained for all patients that received 3-monthly ART packages. These results provide reassurance that stable patients can maintain optimal adherence when provided with an extended ART supply and patients who successfully adhere to treatment in the first two years are ideal candidates for more than one month's supply of treatment. In an overburdened public health care setting, such as South Africa, this practice can ease clinic patient load and reduce the need for monthly clinic visits which impact negatively on patient finances and employment prospects.

High pill burden, regimen complexity and dosing more than once a day are known to hinder adherence. [64] This is evidenced by lower adherence often observed with PI-based regimens. [42, 65-67] Despite the additional pill burden and dosing frequency with switching from a once daily NNRTI-based regimen to a twice daily LPV/r regimen, with almost double the number of pills to be taken, adherence was not impaired and viral load suppression improved significantly in our patients who failed initial treatment. The use of a boosted PI regimen, provision of enhanced adherence counselling to patients on the implications of treatment failure with reinforcement of the importance of good adherence and enlisting a treatment supporter, where possible, may account for the improved outcomes. [68-70]

HIV and TB co-infection rates are highest in South Africa. [71] Concurrent treatment of both diseases reduces morbidity and mortality; however, patients must cope with the additional pill burden and overlapping side effects when taking ART and TB treatment which can lead to impaired or selective adherence to either ART or TB medication. [25, 72, 73] We found no significant changes in ART adherence or viral suppression in our patients on concurrent HIV and TB treatment. This is commensurate with findings from other South African studies. [74]

There are several limitations to our study. This was a retrospective study of ART adherence conducted at a single research site and adherence behaviour may have been influenced by participation in a clinical trial, where patients were routinely monitored and received extensive adherence support and counselling. Hence, adherence in this population may not be generalizable to other population settings. Factors associated with adherence behaviour were limited to available baseline patient and clinical data. Furthermore, not all eligible patients that completed follow up from the SAPiT study were enrolled into the TRuTH study as they were lost to follow up, demised or declined participation. Assessment of adherence by pill count may be prone to bias as non-adherent patients familiar with the pill count assessment may ‘count tablets’ and return the required number of pills to show good adherence. An accurate adherence calculation is not possible for patients who did not bring any remaining pills back, reported lost pills and/or pills left at home.

Optimal long-term adherence rates observed in this cohort support the evidence of high adherence reported in other long-term African cohorts. The durability of first line efavirenz based regimens was demonstrated by high viral suppression rates and low number of treatment failures. Pill count was not a good predictor of viral failure and viral load measurement remains the benchmark for monitoring treatment response. However, adherence during the six months post-ART initiation period has been shown to impact long-term treatment outcomes and viral load is only measured six months after commencement of ART per in-country treatment guidelines and thereafter annually. Therefore, we recommend pill count as a quick, simple measure of adherence at each visit in this critical six-month period to identify patients with early adherence challenges and allow for timeous intervention.

Provision of adherence support measures which may have assisted patient adherence included individual and group counselling, provision of pill boxes, treatment supporters and tracking of patients who missed their clinic appointment date. Pharmacists were also able to identify patients experiencing adherence challenges when conducting pill counts and could either provide or refer patients for appropriate adherence counselling. Further investigation is required into determining which of these adherence support measures are time and cost effective for adoption into our resource limited public health care setting. We also demonstrated that providing stable patients with a 3-month ART supply was feasible as optimal adherence was still maintained over this extended time between clinic visits. This has the potential to reduce clinic workloads and patient time and costs associated with monthly clinic visits and is currently being investigated further in a randomized control trial. [75]

In summary, our study found optimal long-term adherence with good treatment outcomes are possible within a structured ART programme with close adherence monitoring and support. With the implementation of universal test and treat rapid scale up of ART provision, it is imperative that patient adherence is continually monitored and supported to ensure a successful ART programme in South Africa.

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Table 1: Baseline demographics and clinical characteristics

Variable	Total (n=270)
Demographics	
Age(years), median (IQR)	34 (29-40)
Gender (female) (%)	148 (54.8)
Education[a]	
Primary school or less (%)	58 (21.5)
Secondary school not complete (%)	123 (45.6)
Secondary school complete (%)	88 (32.6)
Head of household (%)	179 (66.3)
Primary breadwinner (%)[a]	190 (70.4)
Stable partner (%)	46 (17.0)
Employed, full or part time (%)	164 (60.7)
Access to tap water and electricity (%)[a]	236 (87.4)
Tested for HIV prior to enrolment (%)[b]	134 (49.6)
Disclosed HIV status (%)[b]	154 (57.0)
Clinical Characteristics	
CD4+ count (cells/mm^3)[*], median (IQR)	145 (75-249)
Viral Load (copies/mL)[*], median (IQR)[c]	141 000 (37 757 – 386 000)
WHO Stage	
Stage 3 (%)	254 (94.1)
Stage 4 (%)	16 (5.9)

IQR interquartile range, *WHO* World Health Organization

[a] 1 missing data

[b] 9 missing data

[c] 4 missing data

[*] measured at visit prior to or at initiation of ART

Table 2: Mean adherence to ART by pill count

Time on ART, months	**sample size, n**	**Mean adherence, % (SD)**
≤6	268	97.7 (5.2)
> 6-12	270	98.3 (6.4)
> 12-18	258	99.1 (2.2)
> 18-24	205	99.3 (1.8)
> 24-30	115	99.0 (3.6)
>30-36	161	98.8 (5.2)
>36-42	201	99.2 (3.4)
> 42-48	243	99.0 (4.8)
>48-54	260	98.7 (5.8)
>54-60	268	98.7 (4.3)
>60-66	270	98.8 (4.4)
>66-72	172	98.6 (6.5)
>72	116	98.3 (7.5)

Table 3: Sensitivity and specificity of ART adherence by pill count in predicting viral load suppression

Time on ART (years)	Sensitivity (95% CI)	Specificity (95% CI)
1	97% (94-98)	22% (3-60)
2	98% (95-99)	10% (0-45)
3	97% (94-99)	33% (7-70)
4	98% (96-100)	0
5	95% (91-98)	9% (0-41)

ART antiretroviral therapy

* using 12 months of pill count data before last viral load measurement closest to year of interest

Table 4: ART adherence and VL suppression in HIV-TB co-infected participants and participants switched to second line regimen

	6 month period prior to TB treatment (*n*)	**During anti-TB treatment *(n)***	**6 month period prior to regimen change (*n*)**	**6 months after regimen change *(n)***	**12 months after regimen change[a] (*n*)**
Mean adherence					
< 95%	0	3	7	2	0
≥ 95%	17	14	14	19	19
p-value		0.159		0.012	0.080
Viral load					
> 400 copies/mL	2	3	21	5	1
< 400 copies/mL	15	14	0	16	19
p-value		0.703		<0.05	<0.05

ART antiretroviral therapy, *TB* tuberculosis
VL viral load, ART antiretroviral therapy, *LPV/r* lopinavir/ritonavir
[a] 3 missing data

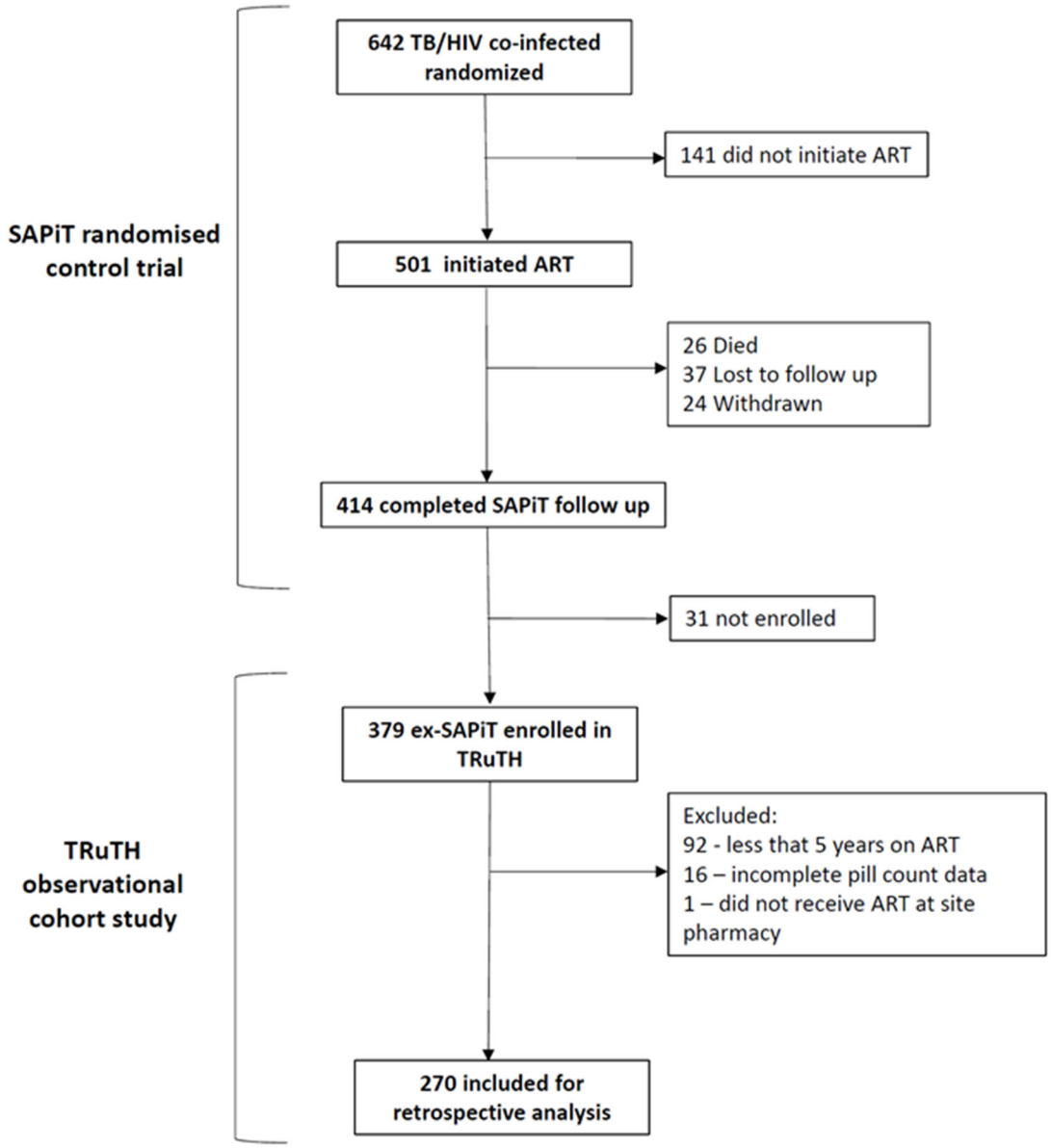


Figure 1. Selection of patient cohort on ART for at least 5 years

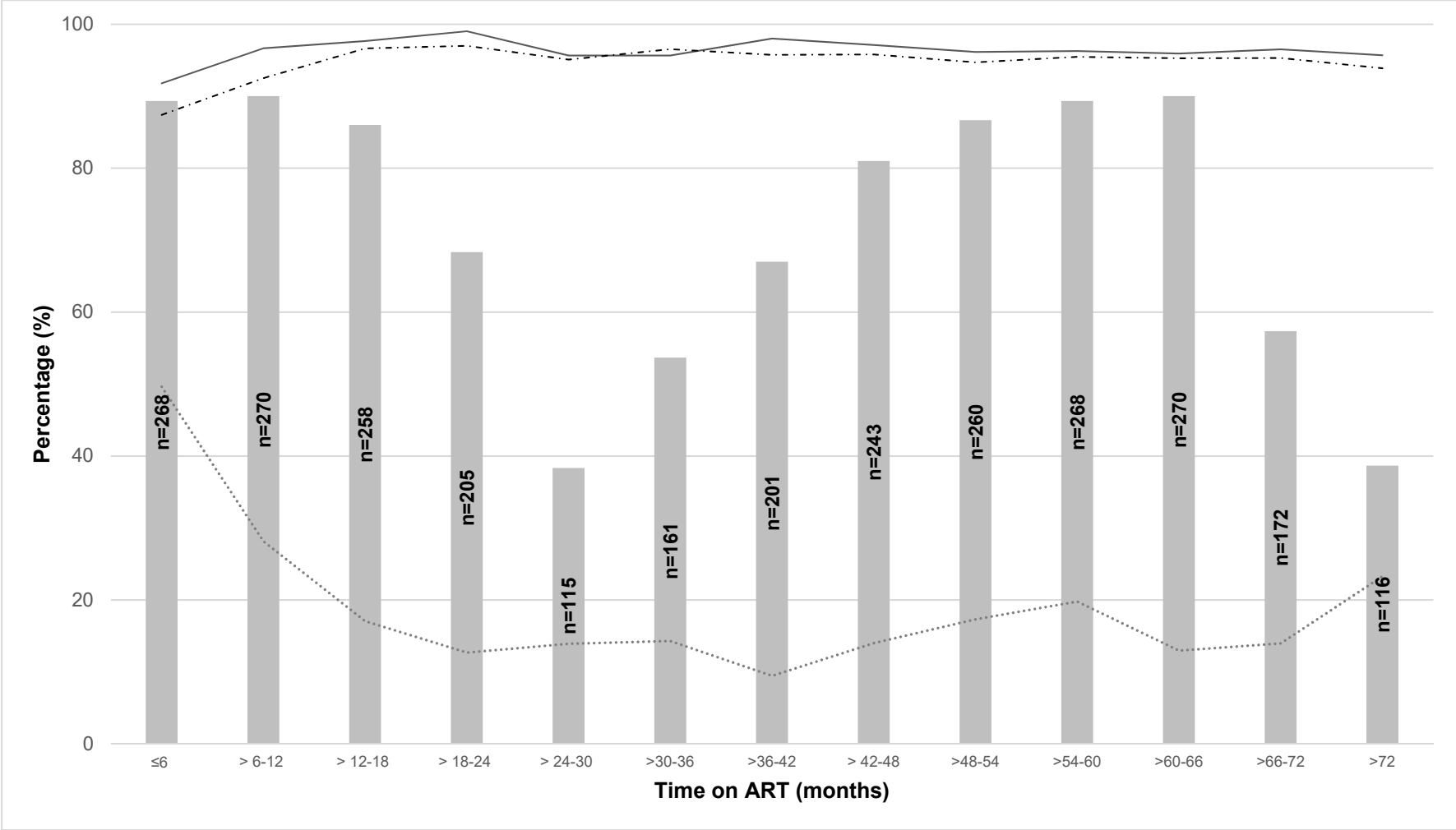
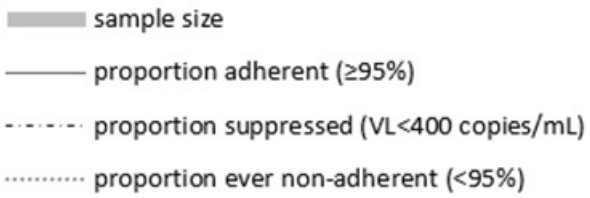
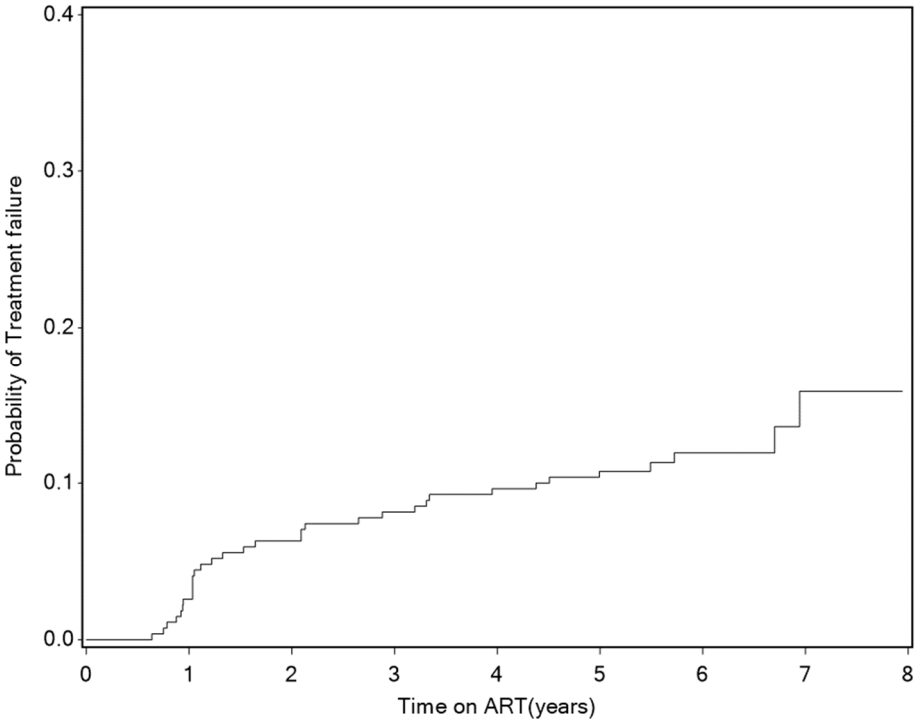


Figure 2. Patient adherence and viral load suppression over duration of follow up period

Figure 2 Legend:





Time on ART (years)	0	2	4	6	8
Number at risk	270	253	244	109	0
Number of treatment failures	0	17	9	5	2

Figure 3. Probability of treatment failure over time

3.2 Discussion of Manuscript

The aim of this manuscript was to assess long term adherence, in patients on ART for five years or longer in an urban adult cohort, and addresses all five primary objectives listed in Chapter 1. Monthly adherence, determined by pharmacy pill count, was assessed and compared to six monthly viral load measurements. Sensitivity and specificity values were calculated for each year on ART to evaluate if pill count was a reliable predictor of virological suppression. Baseline patient and socio-demographic variables were assessed to determine if they were predictive of long term adherence. Changes in adherence was also assessed when patients were switched to a second line regimen. In addition, we examined the impact of concurrent TB and HIV treatment on ART adherence in patients presenting with recurrent TB by analysing changes in adherence and viral load suppression before and during TB treatment.

Overall mean adherence to ART for the entire cohort was ≥ 95% for each year on ART. The proportion of patients with an undetectable viral load (< 400 copies/ml) was 87.4% six months after ART initiation and, thereafter, increased and remained above 92% throughout study follow up. Pill count showed high sensitivity in predicting viral suppression but had poor specificity when the viral load was detectable. There was no association between baseline patient demographics or clinical characteristics and optimal adherence to ART. Despite the higher pill burden, optimal adherence improved and there was a significant increase in viral load suppression at 6 and 12 months after patients were switched to a second line regimen. In patients on concurrent ART and TB treatment there was no significant decline in ART adherence and viral load suppression rates. Stable, virologically suppressed patients who were provided with an extended ART supply were able to maintain excellent adherence with overall mean adherence of 99.5% for all three month ART packages dispensed.

This study demonstrated high long term adherence to ART over a more than five year period. Although pill count was not a good predictor of viral failure, monitoring adherence using pill count is recommended during the critical six month post-ART initiation period to identify patients with adherence challenges as early non-adherence has been shown to increase the risk of virological failure in the long term. In addition, we found that providing stable patients with a three month ART supply was feasible as optimal adherence was maintained over the extended time between clinic visits. Various adherence support strategies were employed to support patient adherence and further research is required into determining which of these adherence support measures are time and cost effective for our resource limited public health care setting. Furthermore, with the implementation of the UTT strategy and rapid scale up of ART, it is essential to assess adherence in the increasing number of patients on ART to determine if the required levels of adherence for successful ART outcomes are

being achieved and maintained. Supplementary data not presented in the manuscript can be found in Appendix O.

3.3 Masters Candidate's contribution to the Manuscript

Student Name: Atika Moosa

Student number: 215046459

Title of the article: Long Term Adherence to Antiretroviral Therapy in a South African Adult Patient cohort

Authors: Moosa A, Gengiah T.N, Lewis L, Naidoo K

Journal: AIDS Patient Care and STDs

Master student's contribution:

1. This retrospective study was completed on data captured in the CAPRISA SAPiT randomized controlled trial and TRuTH observational cohort study. In the TRuTH study, I was involved in conducting pill counts, capturing pill count data on CRFs, dispensing ART and providing counselling to patients on; correct dosing, management of side effects, new ARV drugs or ART regimen changes and the importance of adherence. I was also involved in providing additional adherence counselling to patients identified with adherence challenges.

2. Formulation of Hypothesis

I formulated the study hypothesis in conjunction my supervisor, Tanuja N. Gengiah. I wrote the concept sheet and proposal for this study and submitted it to UKZN Biomedical Research Ethics Committee for approval and ethical clearance.

3. Study Design

I designed the retrospective analysis and selected the variables for analysis with CAPRISA SAPiT study data captured from June 2005 to April 2010 and TRuTH study data captured from November 2009 to April 2014.

4. Data Analysis

To ensure data validity and reliability for the manuscript and dissertation, I reviewed and conducted a clean-up of pill count data. In addition, I reviewed patients' files and added any missing data to the electronic databases. During this process corrected information was verified and updated with the CAPRISA Data Management team. I performed the initial baseline demographic data analysis and Chi Square analysis to determine the association between baseline patient demographics or clinical

characteristics and optimal adherence to ART on SPSS version 25 which were confirmed by the statistician on SAS version 9.4.

5. Write up

As first author, the manuscript was written by me before a final draft was submitted to all co-authors for review and comments. Approval for the final version of the manuscript was received from the three co-authors before submission to the journal, AIDS Patient Care and STDs. I submitted the manuscript for review and publication to this journal on the 22 November 2018 (Appendix C). Originality and non-plagiarism were confirmed by submitting the manuscript to Turnitin on 30 October 2018.

I declare the above to be a true reflection of my contribution to this journal article.

Signature: 

Date: 22 November 2018

CHAPTER FOUR: DISCUSSION

CHAPTER 4: DISCUSSION

4.1 Discussion of findings

HIV is managed as a chronic disease requiring lifelong high adherence to ART to ensure viral suppression, prevent emergence of resistant viral strains and achieve good morbidity and mortality outcomes. The literature review presented in Chapter 1 identified the paucity of information on long term ART adherence in South Africa, which has the largest number of PLWH on ART globally. The aim of this study was to assess long term adherence in patients receiving ART for at least five years or longer in an HIV endemic urban setting in Durban, South Africa.

Pill count is an objective pharmacy adherence measure that has been used in various healthcare settings to monitor adherence. It is quick to complete, requiring no specialized equipment and minimal training which is advantageous in a resource limited setting. In this study, pill count based adherence was assessed at each visit and compared to six monthly viral load measurements. Viral load is currently used to monitor treatment response, however, in the public health sector it is measured less frequently (annually) and results are not immediately available. In this retrospective study we assessed if pill count data was a predictor of virologic outcomes and may be used as a reliable proxy. This could allow the pharmacist or other health care workers to identify and initiate a timeous intervention in patients at risk of viremia and treatment failure. We also investigated other factors reported to influence adherence behaviour, including patient socio-demographics, ARV regimen and pill burden.

The key findings from this study were determined by the objectives discussed below:

Objective 1: Assess and compare adherence by pill count and viral load data

Overall mean pill count adherence to ART was 98.7% in this cohort over a long term follow up period of more than six years. Adherence within the first 6 to 12 months of treatment was 98.3% and was higher than that reported in several African studies ranging from 62 to 95% (51, 71, 118, 216, 219). Adherence levels were maintained at ≥95% for each year of follow up and remained stable, ranging between 98-99% over the six-year period. Long term adherence studies in Botswana, Senegal and Nigeria also found comparably high levels of adherence of 93%, 91% and >95% respectively, although in the Senegalese cohort where adherence was assessed over seven years, adherence dropped below 90% during the initial four years before improving and stabilising at 91% (133, 216, 218, 220).

Intensive pre-ART education and counselling sessions, an ongoing adherence support programme post-ART initiation, provision of pillboxes and use of a standardized once-daily ART regimen, support measures that have been shown to positively influence adherence, may have played a role in helping to attain high adherence in this cohort (224-226). Additionally, enteric coated ddI was used instead of D4T in our first line ART regimen when patients were initiated on ART in the SAPiT

study, due its better side-effect profile, thereby avoiding non-adherence and discontinuation associated with D4T toxicity observed elsewhere (218, 227, 228).

More than 90% of patients in this cohort maintained optimal adherence throughout the follow up period and this proportion was higher than reported in other long term African patient cohorts where the proportion of patients with optimal adherence ranged between 71-75% (133, 216, 217, 220). Overall, studies conducted in the USA and European countries reported lower adherence rates and a lower proportion of patients with optimal adherence, ranging between 44 to 83% over a similar long-term period (28, 72, 121, 123, 212). There may be several reasons for this; patients in developed countries have had longer exposure to ART treatment as it became available about two decades before developing countries, such as in Africa, were able to access treatment. As a result, these patients may have been on older regimens with a higher pill burden and prone to more side effects and toxicity. Additionally, patients exposed to early era ART may have accumulated resistance to one or more ARV drug classes and had to be switched to more complex treatment regimens as new ARV drugs became available.

Viral load was undetectable in 87% of patients at six months and this proportion increased to 92% at 12 months after ART initiation. Only 11 patients had a viral load > 400 copies/mL after five years on ART and 94% of patients were virologically suppressed at the end of the follow up period. Similar long term virologic outcomes have been reported from other studies conducted in South Africa, Botswana, Zimbabwe and the USA (27, 72, 220, 228-230). The cumulative probability of treatment failure was 0.16 and is consistent with treatment failure rates reported in Uganda and other sub-Saharan cohorts (229, 231, 232). The incidence of treatment failures (n=17) were highest in the two years after ART initiation. After the second year, the number of treatment failures declined with each subsequent year on ART. Studies on long term virologic outcomes have found that the risk of viral failure decreases the longer patients remained suppressed on ART and this may account for the high number of treatment failures in the initial two years after ART initiation followed by a decline in subsequent years in our cohort (74, 233, 234). However, despite the improvement in viral suppression rates over time, poor adherence in the initial months of ART treatment (early non-adherence) has been shown to increase the risk of virologic failure in later years (48, 218, 219, 235, 236). This is commensurate with non-adherence by pill count being most frequent in the first six months of ART treatment in our cohort.

Sensitivity was high but specificity was low for the use of pill count adherence as a proxy for viral load outcomes. While some studies have demonstrated an association between pharmacy adherence measures and virologic outcomes others have found poor agreement between the two measures. For instance, a Mozambican study reported pill count to be a reliable indicator of undetectable viral load using an adherence threshold of >95% (78). The combination of pill count and self-reported

adherence was also found to be highly associated with virologic failure in a South African case-control study (110). Similarly, Muyingo et al. (71) reported a significant relationship between 100% DPR and viral suppression in the first year of ART. On the other hand, pharmacy refill adherence measures were poorly predictive of virological failure in a Johannesburg urban clinic cohort, although pill count was reliable in identifying non-adherent patients (237). Goldman et al. (238) investigated the ability of self-report and MPR to predict viral suppression and both adherence measures were found to be poorly correlated with viral load outcomes.

The use of different adherence measures, varying optimal adherence thresholds, timing of viral load measurements, definition of viral load suppression and time on ART all influence the relationship between adherence and virologic outcomes (77, 111, 239). Although we used an adherence threshold of ≥95%, viral suppression has been reported to be attained in patients with 85-94% on long term ART (72). Furthermore, while pill counts can provide a more objective method of adherence assessment, patient manipulation is possible as non-adherent patients may discard or leave behind medication not taken and return the desired number of pills to demonstrate good adherence (37, 73). Although plasma viral suppression is possible with sub-optimal adherence, low-level viral replication continues in the plasma and reservoirs such as the central nervous system and genital tract, the long term effects of which have not been fully elucidated (84, 85). Therefore, high adherence to ART remains key to ensuring the best clinical outcomes.

Objective 2: Determine if baseline socio-demographic variables predict long term adherence behaviour

Baseline patient demographics and socio-economic variables were not predictive of adherence in this cohort (see Appendix O – additional data presented). Lower adherence was observed in females and patients younger than 40 years and adherence was better in patients who were the primary breadwinner, head of a household or employed. However, none of these associations were statistically significant.

Cross-sectional and short term cohort-based adherence studies have reported certain patient characteristics and socio-economic variables can influence adherence. For instance, higher rates of non-adherence were observed in men who were single (49%), unemployed (56%) or had a tertiary education (60%) in a rural patient cohort (116). Van Dyk et al. (124) demonstrated lower adherence was significantly associated with younger age and non-disclosure of HIV status and ART use, whereas Maqutu et al. (240) found ≥95% adherence was better in younger males and older females and lower in older patients with no schooling. In a Kwa-Zulu Natal cohort, patients in urban areas were three times more likely to be adherent compared to those in rural areas and patients with no partner were 80% more likely to report ≥95% adherence, whereas poor socioeconomic conditions were associated with lower adherence (aOR1.56; 95% CI 1.28-1.89) (51). In contrast, a long term

adherence study in South Africa found no relation between patient demographic characteristics and adherence which is consistent with the findings in our study (27).

In resource limited countries, poor socio-economic conditions, unemployment, financial constraints, low level of education and inadequate access to health care and treatment can impair adherence (135, 165, 167, 169). These factors may not have impacted adherence in our cohort as the clinic location was easily accessible through public transport and patients were reimbursed for transportation costs. In addition, patients received pre-ART education and post-ART adherence support and counselling in their local language, isiZulu, by trained counsellors and this may have facilitated adherence in patients with limited education or poor English literacy levels as there was no language barrier between patients and clinic staff.

Objective 3: Determine the effect of ARV regimen change on adherence by assessing pill count and viral load data six months before and after switch to a second line treatment regimen

High pill burden, regimen complexity and dosing more than once a day have been reported to impair adherence (172). This is evidenced by lower adherence often observed with PI-based regimens (28, 42, 123, 216). Patients who experienced treatment failure in our cohort were switched to a second line boosted PI-based regimen consisting of LPV/r plus two NNRTIs. The number of pills in this regimen was almost double compared to the first line regimens. In addition, the dosing frequency changed from once daily to twice daily. The additional pill burden and increase in dosing frequency did not impair adherence and viral load suppression improved significantly in our treatment failure patients. Our findings support similar improved results observed by Murphy et al. (241) on second line treatment outcomes in South Africa. The use of a boosted PI regimen, provision of enhanced adherence counselling to patients on the implications of treatment failure with reinforcement of the importance of good adherence before and after the regimen change and enlisting a treatment supporter, where possible, may account for the improved outcomes (242-245).

Objective 4: Assess ART adherence during episode/s of recurrent TB infection by pill count and viral load data

HIV infected individuals have a 20 to 30 times greater risk for developing active TB disease and this has fuelled the TB epidemic in South Africa where HIV and TB co-infection rates are the highest globally (186). Concurrent treatment of both diseases has been shown to significantly reduce morbidity and mortality (222, 246, 247). However, patients have to cope with the additional pill burden and overlapping side effects when taking ART and anti-TB drugs concomitantly and this may lead to impaired or selective adherence to either ART or TB medication (187, 248). We found no significant changes in ART adherence or viral suppression in patients on concomitant ART and recurrent TB treatment. A study within several different HIV-TB co-infected patient cohorts in South

Africa also found that patients were able to maintain good adherence to both treatments simultaneously (249).

Objective 5: Determine if there are differences in adherence between patients receiving a monthly supply versus three monthly ART supply by pill count

Patients who were virally suppressed, stable on ART and demonstrated good adherence by pill count were sometimes provided with a three month ART supply in the TRuTH study. Two hundred and sixty-seven patients received a three month ART supply at least once and mean adherence for all three month ART packages dispensed was >99% with optimal adherence attained by 97.5% of patients. A subset of patients (n=46) received a three monthly ART supply at three or more study visits and all patients in this group had optimal adherence levels.

In an overburdened public health care setting, providing patients with a two or three month ART supply can ease clinic patient load and reduce the need for monthly clinic visits which impact negatively on patient finances and employment. In line with the need to improve service delivery and alleviate pressure on the over-extended public health sector facilities, South Africa recently introduced the Centralised Chronic Medicine Dispensing and Distribution (CCMDD) programme where stable, virologically suppressed patients on ART for at least 12 months are able to collect their ART medication every two or three months at a private pharmacy, general practitioner, adherence club or community pick up point closest to them (250, 251). Our results provide reassurance that stable patients can maintain optimal adherence when provided with more than a month of ART supply at a time.

4.2 Study Limitations

This is a retrospective study of ART adherence in the SAPiT and TRuTH studies, both of which were conducted at a single research site. Adherence behaviour may have been influenced by participation in a clinical trial, where patients were routinely monitored, counselled, telephonically or physically tracked and reimbursed for study visits. Therefore, adherence in this population may not be generalizable to other population settings.

Investigation of factors associated with adherence behaviour are limited to available baseline patient, socio-economic and treatment data and changes in baseline characteristics over time were not captured to reliably inform their association with adherence post enrolment into the trials. Furthermore, not all eligible patients who completed follow up from the SAPiT study were enrolled into the TRuTH study as some were lost to follow up, demised or declined participation.

Assessment of adherence by pill count can be prone to bias. Non-adherent patients familiar with the pill count assessment may 'count tablets' and return the required number of pills to demonstrate good adherence. In addition, pill count could not be completed if patients did not bring their remaining tablets at a visit and an accurate adherence calculation would not be possible for patients who reported lost pills and/or pills left at home.

4.3 Recommendations for clinical practice

- Pill count was not a good predictor of virologic failure and we recommend viral load measurement as the benchmark for monitoring treatment response. However, adherence during the six months post-ART initiation period has been shown to impact long term treatment outcomes and viral load is not measured within this crucial time, only six months after initiating ART and thereafter annually per in-country treatment guidelines. The incidence of treatment failures was highest in the initial two years after ART initiation in our cohort. Therefore, pill count is valuable as a quick, simple measure of adherence to identify patients with early adherence challenges and allow for timeous intervention.
- Pharmacists are ideally placed to identify patients experiencing adherence challenges using pharmacy adherence measures such as pill count or drug refill dates and can therefore play a key role in either providing or referring patients for appropriate adherence support and counselling.
- Where possible, the provision of adherence support measures such as individual and group ART counselling sessions, provision of pill boxes, the use of treatment supporters and telephonic tracking of patients who miss a clinic appointment date can assist patient adherence.
- Providing an extended ART supply to virally suppressed, stable patients with optimal adherence to ART for longer than a year is an effective strategy to reduce patient visits and clinic workload in our resource strained public health sector.
- The increased pill burden associated with concurrent treatment of drug sensitive TB and ART does not impair adherence to ART. However, adherence support interventions may be required in patients who already have suboptimal adherence prior starting TB treatment.

4.4 Recommendations for future research

Various patient adherence support measures were used in the SAPiT and TRuTH studies and further investigation is required to determine which of these are time and cost effective for adoption into our resource limited public health care setting. We demonstrated that providing stable patients with a three month ART supply was feasible as optimal adherence was still maintained over this extended time between clinic visits. This has the potential to reduce clinic patient load and alleviate time and economic burden on patients in a busy public health care setting and is currently being investigated further in a randomized control trial (252). In addition, outcomes from the CCMDD programme need

to be monitored and reported to determine if patients are remaining in care and are adherent to treatment.

With the expansion of ART access to all PLWH, it is essential to monitor the impact of rapid treatment scale up on long term adherence. Providing adherence support and retaining patients in care is advocated in local treatment guidelines, however, recent data show that only 74% of patients initiated on ART in 2015-2016 remained in care after 12 months (221). Therefore, further research is needed to determine how long term optimal adherence to ART may be successfully maintained with the increasing numbers of PLWH entering care.

Point-of-care viral load measurements can reduce costs and thereby improve access to viral load monitoring in our resource limited health care setting. Ongoing research in this promising field is important to determine if the diagnostic accuracy of point of care viral load results are comparable to current laboratory based viral load monitoring.

4.5 Conclusion

In summary, our study found that optimal long-term adherence with good treatment outcomes are possible within a structured ART programme with close adherence monitoring and support. While pill count was not a reliable standalone predictor of virologic failure in this study, adherence patterns during the initial six months after ART initiation has been shown to impact long term treatment outcomes, therefore, pill count may be used as a quick, simple measure of adherence to identify patients with early adherence challenges and provide the opportunity for timeous adherence interventions. Viral load measurement remains the benchmark for monitoring treatment response as advocated by current guidelines.

With South Africa's adoption of the UTT strategy and rapid scale up of ART provision, it is imperative that patient adherence is continually monitored and supported to ensure a successful ART programme in South Africa.

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CHAPTER FIVE: APPENDICES

Appendix A

APPENDICES

Appendix A: Supervisor / Student Memorandum of Understanding

Supervisor-Student Memorandum of Understanding
Prepared by Prof MJ Chimbari

This memorandum states the responsibilities of the supervisor(s) and postgraduate student and requires both parties to accept the responsibilities by signing.

Details of Student, Supervisors, and Project

Student Name: Atika Moosa
Student Number: 215046459
School: Pharmacy
Degree: Masters in Pharmacy Practice (online)
Supervisor(s): Dr T. Gengah
Research Topic: Long-term adherence to Highly-Active Antiretroviral Treatment
Date 05 JUN 2015

Responsibilities of the Postgraduate Student
While there are many responsibilities carried by a student in pursuing postgraduate studies the following are the minimum expected.

1. Student should identify a research topic acceptable to the supervisor in order to register
2. Student must show commitment to the degree programme and undertake to produce a full proposal within 3 month of registering
3. Student must produce written work that is their best effortt for comments by the supervisor
4. Student should meet at least once per month (in person or through skype) with the supervisor and have the courage to request for such meetings. In all such meetings the student should provide a brief report of their work and take minutes of the discussions and retain such records until the degree has been awarded
5. Students must keep a laboratory manual where all experimental procedures and data are recorded. This laboratory manual remains the property of the university
6. Student must demonstrate the highest level of scientific honesty at all *stages (proposal writing, seeking ethical approval, collecting data, analyzing data and writing thesis or manuscripts)* of the degree programme.
7. Students must familiarize themselves with the university's policy on Plagiarism
8. Students should follow the advice provided by the supervisor and if they choose not to they should discuss the matter with the supervisor immediately
9. Student must always inform the supervisor of their whereabouts
10. Student should keep up to date with literature in their field of study and share any new literature they come across with the supervisor

11. Student must agree to complete studies within the time specified in the CHS handbook for the specific degree programme
12. Student should allow the supervisor to publish their work if they do not do so or show interest one year after graduating on the understanding that the student will be co-author

Responsibilities of the Supervisor

1. Supervisor must support student at all stages of the degree programme *(settling down, proposal writing, ethical applications, data collection, data analysis and write up of thesis or manuscripts)*
2. Supervisor must be sensitive to the overall well-being of the student
3. Supervisor must have good knowledge of the research area of the student
4. Supervisor must be available to the student and should have regular meetings (face to face or by skype) with the student. If the supervisor must be away for an extended period they should identify a co-supervisor to assist the student during that period
5. Supervisor must read work submitted by student for comments and give feedback within 3 weeks depending on the nature of the work submitted
6. Supervisor must be constructively critical to the student's work
7. Supervisor must have sufficient interest in the work of the student
8. In instances of co-supervision the supervisors must avoid confusing the student by giving conflicting opinions/comments. If there are differences in opinion those should be discussed among the supervisors and the student given the agreed opinion.
9. Supervisor should, where funds permit, facilitate arrangements for masters and doctoral students to present a paper or a poster at an international conference as part of training
10. Supervisor must provide an annual progress report on the research and progression of the student to the discipline
11. Supervisor must protect the work of the student by not pre-maturely publishing it or assigning another student to similar work
12. Student must always be the first author of their work and any co-authorship with other people not on the supervision team should be clarified at an early stage of the project

Conflict Resolution

Should there be a conflict or disagreement between supervisor and student which cannot be resolved by the parties involved, then either party can approach the Academic Leader Research or Dean and Head of School (or the College Dean of Research if the Dean and Head of School is one of the conflicting parties) about the conflict. The Dean and Head of School (or College Dean of Research) will then either arbitrate or choose a senior academic of the School not involved in the conflict to arbitrate. The arbitrator's decision is final and cannot be appealed.

Signatures:

Student.....  .....

Supervisor.....N/A.....

Co-Supervisor(s).....  .....

Academic Leader Research or D&HoS.....

Appendix B

Appendix B: BREC Approval Letters

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

22 April 2016

Ms A Moosa (215046459)
Discipline of Pharmaceutical Sciences
School of Health Sciences
atika.moosa@caprisa.org

Protocol: Long term adherence to antiretroviral therapy.
Degree: MPharm
BREC reference number: BE046/16

EXPEDITED APPLICATION

The Biomedical Research Ethics Committee has considered and noted your application received on 29 January 2016.

The study was provisionally approved pending appropriate responses to queries raised. Your response dated 04 March 2016 to queries raised on 03 March 2016 have been noted and approved by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval**.

This approval is valid for one year from **22 April 2016.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.
BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on **10 May 2016.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc supervisor: gengiaht1@ukzn.ac.za
cc postgrad: nenep1@ukzn.ac.za

Biomedical Research Ethics Committee
Professor J Tsoka-Gwegweni (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 2486 **Facsimile:** +27 (0) 31 260 4609 **Email:** brec@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI

RESEARCH OFFICE
BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Westville Campus
Govan Mbeki Building
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Tel: 27 31 2604769 - Fax: 27 31 260-4609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx

30 January 2018

Ms A Moosa (215046459)
Discipline of Pharmaceutical Sciences
School of Health Sciences
atika.moosa@caprisa.org

Dear Ms Moosa

Protocol: Long-term adherence to antiretroviral therapy.
Degree: MPharm
BREC reference number: BE046/16

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	22 April 2018
Expiration of Ethical Approval:	21 April 2019

I wish to advise you that your application for Recertification dated 22 January 2018 for the above protocol has been **noted and approved** by a sub-committee of the Biomedical Research Ethics Committee (BREC) for another approval period. The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The approval will be **ratified** by a full Committee at a meeting to be held on **13 March 2018.**

Yours sincerely

Mrs A Marimuthu
Senior Administrator: **Biomedical Research Ethics**

Appendix C

Appendix C: Response from Journal

Atika Moosa

From: AIDS Patient Care and STDs <onbehalfof@manuscriptcentral.com>
Sent: Thursday, 22 November 2018 6:01 PM
To: Atika Moosa
Subject: AIDS Patient Care and STDs - Manuscript ID APC-2018-0318

22-Nov-2018

Dear Ms. Moosa:

Thank you for submitting your manuscript titled, "Long-Term Adherence to Antiretroviral Therapy in a South African Adult Patient cohort", for consideration by our journal. Manuscripts are triaged by our editorial staff within two weeks; those selected for external review will lead to an editorial decision within another one to two months.

Your manuscript ID is APC-2018-0318.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to Manuscript Central at https://mc.manuscriptcentral.com/aidspatientcare and edit your user information as appropriate.

You can also view the status of your manuscript at any time by checking your Author Center after logging in to https://mc.manuscriptcentral.com/aidspatientcare.

Thank you for submitting your manuscript to AIDS Patient Care and STDs.

Ensure you stay informed. Register to receive email alerts for the Journal(s) that are critical to advancing your work: www.liebertpub.com/liebertconnect (copy/paste the link into your browser).

Sincerely,
AIDS Patient Care and STDs Editorial Office

Appendix D-N: Case Report Forms

Appendix D: Plate #001 and #002 - Demographics

003 - SAPIT DEMO1

CAPRISA 003 Plate - #001 Visit Code ☐ . ☐☐ ☐ (Phase . Visit, Interim #)

Participant ID: 0 0 3 - 1 2 - ☐☐☐☐ (Study - Site - Participant)

Demographics
Page 1 of 2

Visit Date: ☐☐ dd ☐☐☐ MMM ☐☐ yy

1. Date of Birth ☐☐ dd ☐☐☐ MMM ☐☐ yy **OR** Age ☐☐ years

2. Gender Male ☐ ☐ Female

3. Race ***Mark only one***
White ☐ ☐ Coloured
Black ☐ ☐ Indian
Other ☐
Specify _____

4. Head of Household ***Mark only one***
Self ☐ ☐ Partner
Parent ☐ ☐ Grandparent
Other ☐
Specify _____

5. Primary breadwinner in household ***Mark only one***
Self ☐ ☐ Partner
Parent ☐ ☐ Grandparent
Other ☐
Specify _____

6. Current Marital Status ***Mark only one***

Single/never married ☐ ☐ Separated/divorced

Married/stable partner ☐ ☐ Widowed/death of partner → Date of death: ☐☐ dd ☐☐☐ MMM ☐☐ yy

7. Duration with current/last partner ☐☐ years ☐☐ months

Staff Initials ☐☐☐ Date: ☐☐ dd ☐☐☐ MMM ☐☐ yy

Version 1.0

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CAPRISA 003 Plate - #002

Visit Code ☐ . ☐☐ ☐ (Phase . Visit Interim #)

Participant ID: 003 - 12 - ☐☐☐☐ (Study - Site - Participant)

Demographics
Page 2 of 2

Visit Date: ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

8. Occupation of participant ***Mark only one***

Scholar/Student	☐	☐	Employed full time
Employed part-time	☐	☐	Running Household
Unemployed	☐	☐	Other

Specify: _____

9. Education

Mark only one for highest level of education

no schooling	☐	☐	secondary, not complete
primary school, not complete	☐	☐	secondary, complete
primary school, complete	☐	☐	attended college or university

10. How many children do you have? ☐☐

11. Does the house have :	***No***	***Yes***
11a. Tap water	☐	☐
11b. Electricity	☐	☐
11c. Telephone	☐	☐

12. In the house, how many residing.

12a. Children (<18 years)	☐☐
12b. Adults	☐☐

Staff Initials ☐☐☐ Date: ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

Appendix E: Plate #003 – Baseline Behaviour Questionnaire

003 - SAPIT **BEHB1**

CAPRISA 003 Plate - #003 Visit Code ☐ . ☐☐ ☐ (Phase . Visit Interim #)

Participant ID: 0 0 3 - 1 2 - ☐☐☐☐ (Study - Site - Participant)

Behaviour Questionnaire
Baseline
Page 1 of 2

Visit Date: ☐☐ dd ☐☐☐ MMM ☐☐ yy

I will be asking you some personal questions about your sexual health and behaviour during this interview. Your honest answer is very important to us. Please keep in mind that this information will be handled confidentially. This interview will take about 30 minutes. If you have any questions during the course of the interview, you are welcome to interrupt and I will try to clarify. If you do not want to answer a specific question, you are welcome to refuse.

Substance Use - do you currently use:

Mark all	Never	Occasionally	Frequently	If occasionally or frequently, then specify:
1.a. Cigarettes	☐	☐	☐ →	☐☐☐ Cigarettes per **week**
1.b. Alcohol	☐	☐	☐ →	☐☐☐ Units per **week**
1.c. Dagga	☐	☐	☐ →	☐☐☐ Times per **month**
1.d. Injection drugs	☐	☐	☐ →	☐☐☐ Times per **month**
1.e. Other drugs	☐	☐	☐ →	☐☐☐ Times per **month**

If other, specify _____

HIV disclosure

	No	Yes	Refused	
2. Prior to this study, had you ever been tested for HIV?	☐	☐	☐	
3. Have you discussed your HIV status with anyone?	☐	☐	☐	→ *If No or Refused, skip to next page*

4. If YES,with whom have you discussed your HIV status? ***Mark all that apply***

	No	Yes		No	Yes
4.a. Husband/Wife/Primary Partner	☐	☐	4.g. Extended Family	☐	☐
4.b. Casual Partner (sexual)	☐	☐	4.h. Work Colleague	☐	☐
4.c. Child	☐	☐	4.i. Employer	☐	☐
4.d. Neighbour	☐	☐	4.j. Friend	☐	☐
4.e. Parent	☐	☐	4.k. Other	☐	☐
4.f. Sibling	☐	☐	Specify _____		

5. Overall how would you describe their response to learning about your HIV status? ***Mark only one***

Completely Supportive	Somewhat Supportive	Somewhat Unsupportive	Completely Unsupportive
☐	☐	☐	☐

6. Since the day you found out about your HIV status, how long was it (in days or months) until you discussed your HIV status with someone else (other than your health care worker or counsellor)?

☐☐☐ months ☐☐ days *Complete total number of months and/or days; if no months or no days, enter a "0"*

Signature: _____

Staff Initials ☐☐☐ Date ☐☐ dd ☐☐☐ MMM ☐☐ yy

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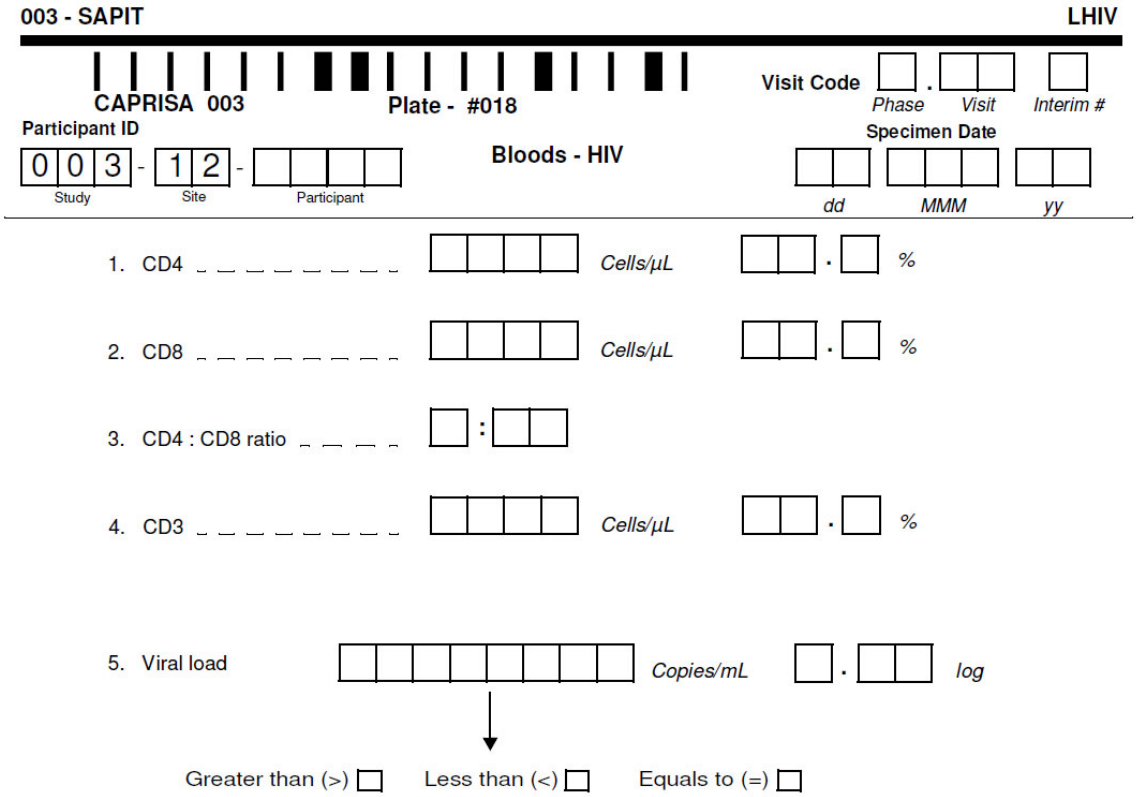
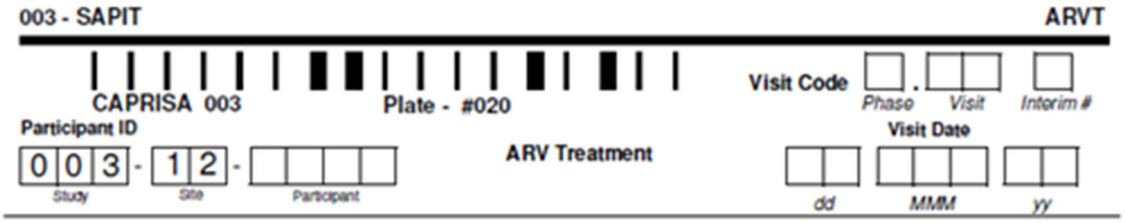
Appendix F: Plate #018 – Bloods – HIV



Appendix G: Plate #020 – ARV Treatment



	ARV Treatment*	Dosage (mg)	Dispense daily	Dispense bd	Date started dd	Date started MMM	Date started yy	Date stopped dd	Date stopped MMM	Date stopped yy
1.										
2.										
3.										
4.										

* See chart for codes for ARV drugs

Specify reason for interruption of ARV (if relevant):

1. _____

2. _____

3. _____

4. _____

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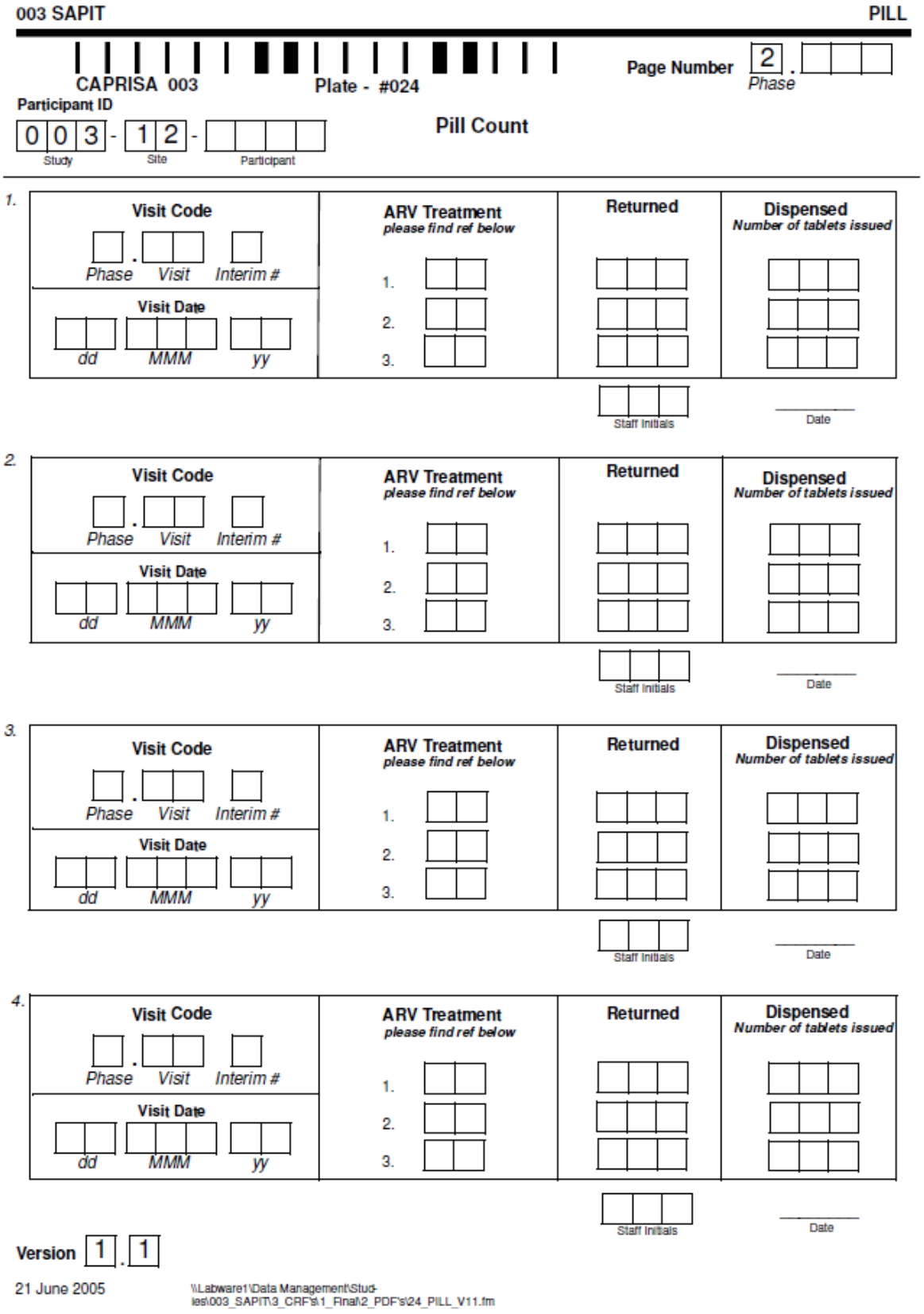
Staff Initials

Date (dd MMM yy)

Appendix H: Plate #024 and #063 – Pill Count



003 SAPIT — PILL

CAPRISA 003 — Plate - #024 — Page Number 2 . ___ (Phase)

Participant ID: 0 0 3 - 1 2 - ____ (Study - Site - Participant)

Pill Count

	Visit Code (Phase . Visit / Interim #)	Visit Date (dd MMM yy)	ARV Treatment (please find ref below)	Returned	Dispensed (Number of tablets issued)
1.			1. 2. 3.		
2.			1. 2. 3.		
3.			1. 2. 3.		
4.			1. 2. 3.		

Staff Initials ____ Date ____

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CAPRISA 003 Plate - #063

Page Number 2 . Phase

Participant ID

0 0 3 - 1 2 - Study Site Participant

Pill Count

1. Staff Initials ____ Date ____

Visit Code (Phase . Visit, Interim #) / Visit Date (dd MMM yy)	ARV Treatment *please find ref below*	Tablets Lost	Reported tablets remaining	Returned (physical)	Issued *Dispensed + re - Issued*
	1.				
	2.				
	3.				

2. Staff Initials ____ Date ____

Visit Code (Phase . Visit, Interim #) / Visit Date (dd MMM yy)	ARV Treatment *please find ref below*	Tablets Lost	Reported tablets remaining	Returned (physical)	Issued *Dispensed + re - Issued*
	1.				
	2.				
	3.				

3. Staff Initials ____ Date ____

Visit Code (Phase . Visit, Interim #) / Visit Date (dd MMM yy)	ARV Treatment *please find ref below*	Tablets Lost	Reported tablets remaining	Returned (physical)	Issued *Dispensed + re - Issued*
	1.				
	2.				
	3.				

4. Staff Initials ____ Date ____

Visit Code (Phase . Visit, Interim #) / Visit Date (dd MMM yy)	ARV Treatment *please find ref below*	Tablets Lost	Reported tablets remaining	Returned (physical)	Issued *Dispensed + re - Issued*
	1.				
	2.				
	3.				

1= Efavirenz = EFV
2= Lamivudine = 3TC
3= Didanosine = ddI
4= Nevirapine = NVP
5= Abacavir = ABC
6= Lopinavir = Lpv/r
7= Stavudine = D_4T
8= Saquinivir = Sqv
9= Ritonivir = RTV
10= Zidovudine = AZT
11= Indinivir = IDV
12= Combivir = 3TC/AZT
13= Didanosine = ddI-EC
14= Tenofivir = TDF
15= Aluvia = Lpv/r

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Appendix I: Plate #030 and #031 – WHO Staging

003 - SAPIT WHO1

CAPRISA 003 Plate - #030

Visit Code ☐ . ☐☐ ☐ (Phase . Visit Interim #)

Participant ID

0 0 3 - 1 2 - ☐☐☐☐ (Study - Site - Participant)

WHO Staging
Page 1 of 2

Visit Date ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

Clinical Stage 1

	No	Yes
1. Acute retroviral infection	☐	☐
2. Asymptomatic	☐	☐
3. Persistent generalized lymphadenopathy (enlargement of the lymph nodes)	☐	☐

Clinical Stage 2

	No	Yes
4. Weight loss, <10% of body weight	☐	☐
5. Minor mucocutaneous manifestations (seborrhoeic dermatitis, prurigo (chronic itchy skin), fungal nail infections, recurrent oral ulcerations, angular cheilitis (inflammation of the corners of the mouth)	☐	☐
6. Herpes zoster (shingles), within the last 5 years	☐	☐
7. Recurrent upper respiratory tract infections (i.e. bacterial sinusitis)	☐	☐

Clinical Stage 3

	No	Yes
8. Weight loss, >10% of body weight	☐	☐
9. Unexplained chronic diarrhea, >1 month	☐	☐
10. Unexplained prolonged fever (intermittent or constant), >1 month	☐	☐
11. Oral candidiasis (thrush)	☐	☐
12. Vulvo-vaginal candidiasis, chronic (>1 month) or poorly responsive to therapy	☐	☐
13. Oral hairy leukoplakia (thickening of the dorsal surface of the tongue)	☐	☐
14. Pulmonary tuberculosis, within the past year	☐	☐
15. Severe bacterial infections (e.g. pneumonia)	☐	☐

Staff Initials ☐☐☐ Date ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

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CAPRISA 003 Plate - #031

Visit Code ☐ . ☐☐ ☐ (Phase . Visit Interim #)

Participant ID

0 0 3 - 1 2 - ☐☐☐☐ (Study - Site - Participant)

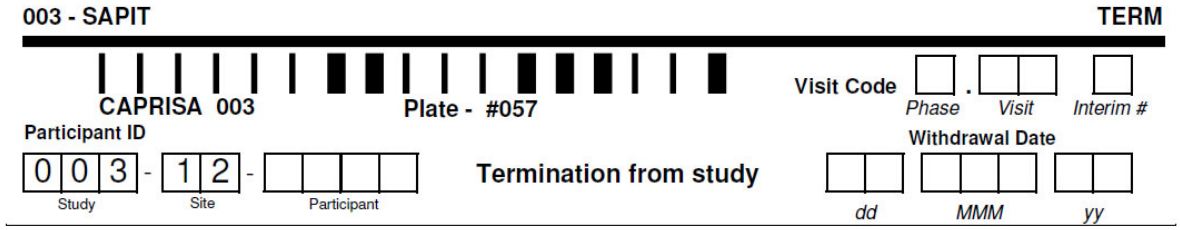
WHO Staging
Page 2 of 2

Visit Date ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

Clinical Stage 4

	No	Yes
16. HIV wasting syndrome, as defined	☐	☐
17. Pneumocystis carinii pneumonia	☐	☐
18. Toxoplasmosis of the brain	☐	☐
19. Cryptosporidiosis with diarrhea, >1 month	☐	☐
20. Cryptococcosis, extrapulmonary	☐	☐
21. Cytomegalovirus (disease of an organ other than liver, spleen or lymph nodes)	☐	☐
22. Herpes simplex virus infection, mucocutaneous >1 month, or visceral (any duration)	☐	☐
23. Progressive multifocal leuko-encephalopathy (selective destruction of the central nervous system)	☐	☐
24. Any disseminated endemic mycosis (i.e. histoplasmosis, coccidioidomycosis)	☐	☐
25. Candidiasis of the oesophagus, trachea, bronchi or lungs	☐	☐
26. Atypical mycobacteriosis, disseminated	☐	☐
27. Non-typhoid salmonella septicaemia	☐	☐
28. Extrapulmonary tuberculosis	☐	☐
29. Lyphoma	☐	☐
30. Kaposi's sarcoma	☐	☐
31. HIV encephalopathy, as defined	☐	☐

Appendix J: Plate #057 - Termination from study



1. Reason for termination *Mark only one*

- Completed study ☐
- Lost to follow-up ☐
- Withdrawal of consent/request of subject ☐
- Withdrawn for discovery of pre-existing violation of entry criteria ☐
- Withdrawn for protocol non-compliance ☐
- Withdrawn for adverse signs and symptoms ☐
- Study is not in best interest of patient as judged by clinician ☐
- Withdrawn for any other reason ☐ → 1.a. Specify : _____
- At the discretion of the Ethics Committee ☐
- Patient deceased ☐ → 1.b. Date of death ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

1.c. Primary cause of death _____

_____

1.d. Is the death suspected to be due to an AIDS-defining condition? *No* ☐ *Yes* ☐

2. If participant left the study, did he/she continue ART at another site? *No* ☐ *Yes* ☐ *Unknown* ☐

Comments _____

_____

_____

Staff Initials ☐☐☐ Date ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

Version 1.0

27 April 2005

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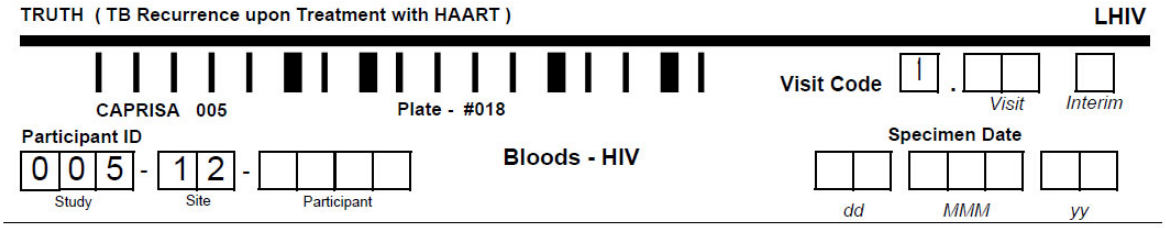
Appendix K: Plate #018 – Bloods – HIV



1. CD4 _ _ _ _ _ _ _ _ _ Cells/µL . %

2. CD8 _ _ _ _ _ _ _ _ _ Cells/µL . %

3. CD4 : CD8 ratio _ _ _ _ _ :

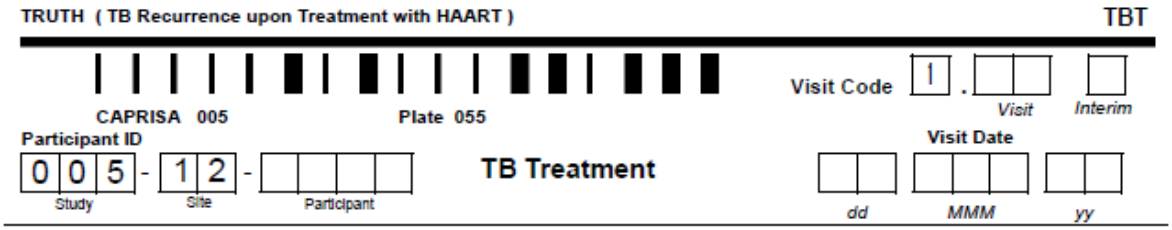
4. CD3 _ _ _ _ _ _ _ _ _ Cells/µL . %

5. Viral load Copies/mL . log

5a. Greater than (>) ☐ Less than (<) ☐ Equals to (=) ☐ Undetectable ☐

5b. Type of assay _ _ _ ☐ Roche RT - PCR (TaqMan)

Appendix L: Plate #055 – TB Treatment



1. Date TB diagnosed ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

2. Date TB treatment started ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

3. Date TB continuation phase started / IP ended ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

4. Date TB therapy ended ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

5. TB diagnosis made on basis of : *(Mark all that apply)*

Chest- X-ray	☐	Sputum smear	☐
Sputum culture	☐	Histology	☐
Clinical	☐	Other	☐

If *Other,* specify : _____

6. Outcome of TB therapy (*Mark only one)*

Cure	☐	Failure	☐
Successful completion	☐	Treatment Interruption	☐
Lost to follow - up	☐	Died	☐
Moved away/Relocated	☐	Transferred out	☐
Other	☐		

If *Other,specify* _____

Remember that MDR or XDR TB is not an outcome

Staff Initials ☐☐☐ Date ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

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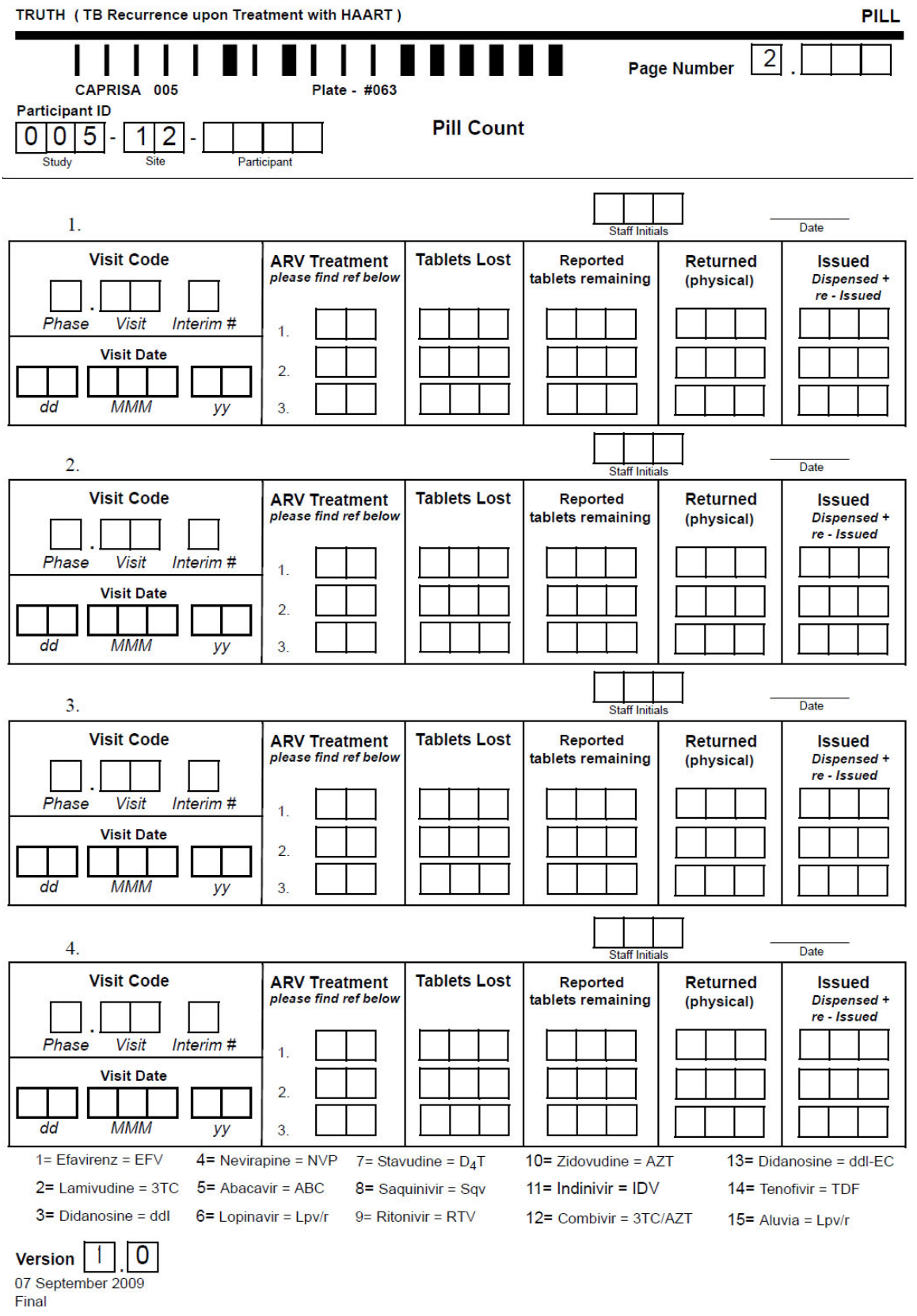
Appendix M: Plate #063 – Pill Count



TRUTH (TB Recurrence upon Treatment with HAART)

PILL

CAPRISA 005 Plate - #063

Page Number 2 .

Participant ID

0 0 5 - 1 2 - Study / Site / Participant

Pill Count

1. Staff Initials ___ Date ___

Visit Code (Phase . Visit, Interim #) / Visit Date (dd MMM yy)	ARV Treatment *please find ref below*	Tablets Lost	Reported tablets remaining	Returned (physical)	Issued *Dispensed + re - Issued*
	1.				
	2.				
	3.				

2. Staff Initials ___ Date ___

Visit Code (Phase . Visit, Interim #) / Visit Date (dd MMM yy)	ARV Treatment *please find ref below*	Tablets Lost	Reported tablets remaining	Returned (physical)	Issued *Dispensed + re - Issued*
	1.				
	2.				
	3.				

3. Staff Initials ___ Date ___

Visit Code (Phase . Visit, Interim #) / Visit Date (dd MMM yy)	ARV Treatment *please find ref below*	Tablets Lost	Reported tablets remaining	Returned (physical)	Issued *Dispensed + re - Issued*
	1.				
	2.				
	3.				

4. Staff Initials ___ Date ___

Visit Code (Phase . Visit, Interim #) / Visit Date (dd MMM yy)	ARV Treatment *please find ref below*	Tablets Lost	Reported tablets remaining	Returned (physical)	Issued *Dispensed + re - Issued*
	1.				
	2.				
	3.				

1= Efavirenz = EFV
2= Lamivudine = 3TC
3= Didanosine = ddI
4= Nevirapine = NVP
5= Abacavir = ABC
6= Lopinavir = Lpv/r
7= Stavudine = D_4T
8= Saquinivir = Sqv
9= Ritonivir = RTV
10= Zidovudine = AZT
11= Indinivir = IDV
12= Combivir = 3TC/AZT
13= Didanosine = ddI-EC
14= Tenofivir = TDF
15= Aluvia = Lpv/r

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Appendix N: Plate #057 -Termination from study

TRUTH (TB Recurrence upon Treatment with HAART) **TERM**

CAPRISA 005 Plate - #057 Visit Code 5.99 (Visit) 9 (Interim)

Participant ID 005 - 12 - ____ (Study - Site - Participant)

Termination from study

Withdrawal Date ____ (dd) ____ (MMM) ____ (yy)

1. Reason for termination ***Mark only one***

- Completed study _____ ☐
- Lost to follow-up _____ ☐
- Withdrawal of consent/request of subject ___ ☐
- Terminated for discovery of pre-existing violation of entry criteria _____ ☐
- Terminated for adverse signs and symptoms__ ☐
- Study is not in best interest of patient as judged by clinician _____ ☐
- Relocated _____ ☐
- Terminated for any other reason _____ ☐ → 1.a. Specify :_____
- At the discretion of the Ethics Committee _____ ☐
- Patient deceased _____ ☐

1.b. Date of death ____ (dd) ____ (MMM) ____ (yy)

1.c. Primary cause of death _____

1.d. Is the death suspected to be due to an AIDS-defining condition? ***No*** ☐ ***Yes*** ☐

1e. How was death established? ☐ Verbal family/friend ☐ Hospital records ☐ Verbal-Medical professional ☐ Death certificate

1.f. Is copy of death certificate on file ? ***No*** ☐ ***Yes*** ☐

2. If participant left the study, did he/she continue ART at another site? ***No*** ☐ ***Yes*** ☐ ***Unknown*** ☐

Comments _____

_____

Staff Initials ____ **Date** ____ (dd) ____ (MMM) ____ (yy)

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Appendix O

Appendix O – Supplementary Data

Association of demographics, socio-economic conditions and clinical characteristics to ART adherence

Variable	<95% (n=14)	≥95% (n=256)	p-value
Gender			
Female	9	139	0.465
Male	5	117	
Age			
20-25	3	28	0.221
25-40	10	166	
≥40	1	62	
Head of household			
Partner	1	10	0.465
Self	8	171	
Parent	5	57	
Other	0	18	
Primary breadwinner[a]			
Self	7	183	0.149
Partner	2	11	
Parent	4	48	
Other	0	14	
Current marital status			
No partner	14	210	0.082
Stable partner	0	46	
Occupation of patient			
Student	0	6	0.090
Employed	5	159	
Unemployed	9	91	
Education[a]			
Primary school or less	3	55	0.934
Secondary school not complete	7	116	
Secondary school complete	4	84	
Telephone[a]			
Yes	1	55	0.196
No	13	200	
Access to both tap water and electricity[a]			
Yes	12	224	0.813
No	2	31	
Number of adults and children[b]			

Variable	<95% (n=14)	≥95% (n=256)	p-value
<5	9	189	0.572
6-10	4	53	
>10	0	10	
Tested for HIV prior study[c]			
Yes	10 (71.4)	124 (50.2)	0.122
No	4 (28.6)	123 (49.8)	
Disclosed HIV status[c]			
Yes	10 (71.4)	144 (58.3)	0.331
No	4 (28.6)	103 (41.7)	
CD4+ count (cells/mm^3)[d]			
≤50	2	48	0.952
51-200	7	119	
201-350	3	61	
>350	2	28	
Viral load (copies/mL)[d]			
≤5000	0	20	0.182
5001-30000	4	35	
30001-100000	4	52	
>100000	5	146	
WHO staging			
stage3	13	241	0.843
stage4	1	15	

[a] 1 missing data
[b] 5 missing data
[c] 9 missing data
[d] 4 missing data
ART – antiretroviral therapy
WHO – World Health Organization