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THE INFLUENCE OF ART ON ADHERENCE TO TB TREATMENT IN PATIENTS USING THE 'eMUM' ELECTRONIC DOSE MONITORING TOOL – A PILOT STUDY

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of
Master of Science in Medicine in Pharmacotherapy
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I, Marlene Knight, declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Science in Medicine in Pharmacotherapy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.



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ABSTRACT

Health care workers are often reluctant to start anti-retroviral therapy (ART) in patients on *Mycobacterium tuberculosis* (TB) treatment. Reasons include fear of reduced adherence in response to the high pill burden of concomitant TB treatment and ART, risk of Immune reconstitution inflammatory syndrome (IRIS) and cumulative side effects. On the other hand, earlier initiation of ART leads to more rapid restoration of the immune-competence needed to cure the tuberculosis and the enhancement of immune responses to other specific pathogens thereby reducing the risk of opportunistic infections. Health care workers want patients to be adherent as it improves patient outcome, prevents the spread of TB, decreases the risk for treatment failure, prevents the emergence of multi-drug resistant and extensively drug resistant TB and reduces cost of treatment. The aim of this study was to measure whether adherence to TB medication changes when ART is added to a patient's TB medication regimen. Consented adults (>18years) diagnosed with pulmonary TB and Human Immunodeficiency Virus (HIV) co-infection were enrolled in the study. Study participants were followed from one month before initiating ART and for the first month that the patient was taking ART. Adherence was measured before and after starting ART using an electronic dose monitoring ('eMUM') tool, pill count and patient self-report. The study results shows that the change in adherence is not statistically significant and health care workers can thus confidently prescribe ART in patients on TB treatment, without fear of decline in patient adherence.

DEDICATION

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NOMENCLATURE

ART	anti-retroviral therapy
ARV	antiretroviral
ATV	atazanavir
AZT	zidovudine
CAMELIA	Cambodian Early versus Late Introduction of Antiretrovirals
CD4	cluster of differentiation 4
CI	Confidence interval
D4T	stavudine
ddI	didanosine
DOT	direct observation treatment
E	ethambutol
EFV	efavirenz
eMUM	electronic dose monitoring
FTC	emtricitabine
g	gram
H	Isoniazid (when used in RHZE)
HIV	human immunodeficiency virus
InSTI	Integrase inhibitor (integrase strand transfer inhibitor)
IRIS	immune reconstitution inflammatory syndrome
LPV	lopinavir
LPV/r	lopinavir/ritonavir
MDR	multi-drug resistant
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTIs	nucleoside reverse transcriptase inhibitors
NVP	nevirapine
PIs	protease inhibitors
R	rifampicin
RAL	raltegravir
RH	Rifinah®
RHZE	Rifafour®/Rifinah®
SAPIT	Starting Antiretroviral Therapy at Three Points in Tuberculosis

STRIDE	A Strategy Study of Immediate Versus Deferred Initiation of Antiretroviral Therapy for AIDS Disease-Free Survival in HIV-Infected Persons Treated for Tuberculosis with CD4
SQV	saquinavir
SQV/r	saquinavir/ritonavir;
TB	*Mycobacterium tuberculosis*
3TC	lamivudine
TDF	tenofovir
WHO	World health organization
XDR	extensively drug resistant
Z	pyrazinamide

1. INTRODUCTION

1.1 Tuberculosis

Tuberculosis (TB) is caused by an infection with *Mycobacterium tuberculosis* that is transmitted via respiratory route from a person who has active pulmonary TB (The South African National TB Guidelines, 2008). This airborne disease is spread easily in highly populated areas and can lead to progressive, active disease or a silent, latent infection. The disease causes tissue destruction and can lead to death if not treated or inappropriately treated. Latent TB infection can be reactivated years after the primary infection occurred. The disease can cause atypical signs and symptoms in the immune-compromised and progress rapidly in these patients. The T-lymphocytes are responsible for controlling TB infections and because cluster of differentiation 4 (CD4) cells are depleted in HIV-infected patients, these patients are more susceptible to TB infection. TB suspects should be isolated or wear masks to prevent the spread of the disease (Peloquin, 2008, p.1845).

1.2 Tuberculosis in South Africa

South Africa is a high tuberculosis burden country (third highest in world according to the 2011 National Strategic Plan) with a death rate of 49 per 100,000 in 2011. In 2011, there were 500,000 new TB cases in South Africa corresponding to an incidence of 993 per 100,000 populations (Global Health Facts, 2012). Poverty contributes to the high incidence in South Africa. Around 80% of South Africans are infected with the TB bacillus, but the percentage of people that progress to active TB depends to a large degree on their HIV status. A HIV-negative person has a 10% chance to develop TB in their lifetime, while a HIV-positive person has a 10% annual risk to develop TB (Department of Health, 2011).

1.3Tuberculosis treatment

In South Africa, the standard treatment for a TB patient that has never been treated for TB in the past or who has taken TB treatment for less than four weeks, consists of a 2 month intensive phase followed by a 4 month continuation phase (Table 1). The four drugs taken daily in the intensive active phase are rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E). Two of these drugs are taken daily in the continuation phase, namely Rifampicin and Isoniazid. The patient becomes non-infectious after completion of the intensive phase and relapse is prevented by completion of the sterilizing effect of the continuation phase.

Table 1: Regimen 1 (New Cases) (Department of Health, 2011, p.39)

Pre-treatment body weight	**Intensive Phase 7 days a week for 2 months**	**Continuation Phase 7 days a week for 4 months**	
	RHZE (150,75,400,275)	RH (150,75)	RH (300,150)
30-37 kg	2 tablets	2 tablets	
38-54 kg	3 tablets	3 tablets	
55-70kg	4 tablets		2 tablets
>70 kg	5 tablets		2 tablets

Retreatment patients are TB patients who were treated for 4 weeks or more in the past, but have failed treatment, relapsed or returned after defaulting. They are treated with regimen 2 (Table 2) (Department of Health, 2011, p.39). Some clinicians prescribe TB treatment for 9 months in patients co-infected with HIV (Peloquin, 2008, p.1846).

Table 2: Regimen 2 (Retreatment Cases) (Department of Health, 2011, p.39)

Pretreat-ment body weight	**Intensive Phase 7 days a week for 2 months**		**Intensive phase 7 days a week for 1 month**	**Continuation phase 7 days a week for 5 months**			
	RHZE (150, 75, 400, 275)	Strepto -mycin (g)	RHZE (150,75, 400, 275)	RH (150, 75)	E (400)	RH (300, 150)	E (400)
30-37 kg	2 tablets	0.5	2 tablets	2 tablets	2 tablets		
38-54 kg	3 tablets	0.75	3 tablets	3 tablets	2 tablets		
55-70 kg	4 tablets	1.0	4 tablets			2 tablets	3 tablets
>71 kg	5 tablets	1.0	5 tablets			2 tablets	3 tablets

1.4 Adherence defined

Adherence to (or compliance with) a medication regimen is generally defined as the extent to which a patient takes his/her medication as prescribed by his/her healthcare provider. “Adherence to” is the preferred terminology because “compliance with” could be interpreted as if the patient is merely following doctor’s orders instead of the doctor and patient working together to achieve a common goal: the best health outcome for the patient. (The South African National TB Guidelines, 2008). To achieve the best health outcome, the correct dose should be taken at the recommended time of day for the duration required. The patient should not merely be following doctor’s orders, but should rather work with the doctor to achieve the best health outcome for him-/her. This partnership between doctor and patient is better described by the term concordance.

1.5 Benefits of adherence

Clearly, adherence together with patient retention and a healthy lifestyle reduces disability and is a major predictor of survival. "*The healthy adherer"* is a term that emerged from the observance that a patient that is adherent to any placebo or beneficial drug therapy generally leads a healthier lifestyle and according to meta-analysis done by Simpson *et al.* (2006) has a 50% lower mortality rate.

In addition to improving patient outcome, adherence is important as it prevents the spread of *M. tuberculosi*s, decreases the risk for treatment failure, prevents emergence of Multi-Drug Resistant (MDR-TB) and Extensively Drug Resistant TB (XDR-TB), and reduces cost of treatment. Research by the Tuberculosis Epidemiology and Intervention Research Unit of the South African Medical Research Council, has shown that MDR-TB and XDR-TB are prevalent in all the provinces in South Africa. In 2010 South Africa had 7,386 laboratory confirmed MDR-TB cases and 741 confirmed cases of XDR-TB (Department of Health, 2011, p.24). Treatment for MDR and XDR-TB could last for more than 24 months (Snyders, 2009). The cost to treat a re-infected patient is much higher than the standard treatment for a first time infection (The South African National TB Guidelines, 2008).

1.6 Adherence statistics

Nonetheless a quantitative review of journal articles from 1948 through to 1998, excluding institutionalized patients and studies of adherence to community-based programs showed that three in four patients are adherent to medication regimens (DiMatteo, 2004). It was found that across the entire spectrum of diseases reviewed, adherence were highest in HIV/AIDS with an 88% average adherence rate and lowest in sleep disorders with an 66% average adherence rate. However, TB was not one of the diseases included in this review. The higher adherence rate in HIV/AIDS could be attributed to the effort invested in counselling the patients

prior to starting treatment. This proved DiMatteo's hypothesis that patients with a more severe disease are more adherent as the consequences of non-adherence could be more severe or fatal.

1.7 Reasons for non-adherence

Why then are patients not adhering to their drug regimen when it is clearly such an important matter? Some patients are in denial and do not believe that they have TB. As soon as the symptoms are cleared (which can be very early in treatment) patients may stop taking their medication (Munro *et al*., 2007) A similar scenario often occurs when a patient does not understand what TB is or the importance of finishing the course of treatment (Cayla *et al*., 2009). Traditional beliefs (involving the therapies offered by traditional healers), and alcoholism hinder adherence. Poor health infrastructure could be a barrier when medication is unavailable or patients have to wait in long queues or are turned away (The South African National TB Guidelines, 2008). Socioeconomic status can be a barrier as adherence to 6 months of treatment results in transportation costs and missed opportunities to work at whilst attending clinic visits. The medication itself may be a barrier to adherence because of the side effects, high pill burden and long duration of treatments. Social stigmatism may lead to disclosure issues which in turn cause patients to leave their medication behind when visiting relatives. Older patients may forget to take their medication, vision changes with age may make it difficult to read medication bottles and arthritis can make it difficult to open medication bottles (Munro *et al*., 2007). Direct Observation Treatment (DOT) is a facilitator of adherence, but the downside of DOT is that the supporter might not be available to the patient for the entire six month treatment duration or; the supporter might not be as reliable as was expected and might be unavailable at the hour of day when the patient would have preferred to take the medication. Some patients reported that they are not in favour of DOT as they do not feel comfortable with somebody 'checking up on them' (The South African National TB guidelines, 2008).

1.8 Adherence facilitators

The South African National Tuberculosis Guidelines (2008) contains many strategies to facilitate adherence. It encourages counselling on treatment and importance of adherence, but warns that difficulties should be anticipated and dealt with proactively.

- Family: A supportive family structure can motivate a patient to be adherent.
- One-stop service providers: The capacity of community systems should be strengthened so that quality, efficient attention may be provided at a one-stop service provider. Integration strategies like these have made it possible to better prepare patients that are started on TB treatment for ART initiation and the clinicians are more aware of drug interactions, adverse effects and Immune Reconstitution Inflammatory Syndrome (IRIS) while the patient spent less time travelling and waiting to be attended to (Friedland, Harries and Coetzee, 2007).
- Faith and health care: It might be of benefit to couple the institutions from the faith-based sectors with health care infrastructure.
- Cost and time to patient to obtain treatment should be kept at a minimum.
- The treatment should be simplified by providing once daily fixed dose treatment in blister packs as far as possible.
- Reminders like short message system communications, pill box organizers and beeper boxes facilitate adherence.
- DOT: To facilitate adherence, the South African TB control program advocate the use of DOT where an observer (clinic staff, community treatment supporter or workplace supporter) observes the patient taking their medication in a way that is sensitive and supportive to the patient's needs. This type of support allows effective monitoring of adherence and early pick-up of patient's non-adherence and adverse drug effects. DOT has the potential to build good relationships between employees and

employers but might involve some training to start off the monitoring process and requires disclosure between employee and employer. The most convenient time and place for DOT should be chosen such as to improve adherence (The South African National TB Guidelines, 2008).

1.9 Reasons to monitor adherence

Adherence lapses often precede treatment failure, so detecting them early provides an opportunity for improvement in adherence that could prevent bacteriological resistance (Munro *et al*., 2007). As a result many methods of adherence monitoring have been developed. An accurate measurement of adherence is essential for targeting and rigorously evaluating interventions to improve adherence and minimize regimen failure (Haberer, 2012).

1.10 Electronic monitoring of adherence

Vriesendorp *et al*. (2007) conducted a study in newly diagnosed HIV patients in Botswana, where they found that it is feasible to assess ART adherence of patients living in a low resource setting with electronic monitors. The Micro Electro Mechanical Systems (MEMS) IV Track Cap devices were used in this study. This blinded pilot study consisting of 30 patients, found a significant difference between the data recorded through electronic monitors and self-reporting with a mean of 85% and 98% respecively. There was a wide range from 21-100% in the adherence level measured with the electronic device. Electronic monitoring devices are limited by patient honesty as it only records the time of opening the lid and not the number of tablets taken out and whether or not medication was in fact consumed. It might be a bit of a learning curve for both patient and health care provider to use the system.

In the current study, ‘eMUM’ was used (Figure 1). It is an electronic medical usage monitoring tool that compiles dosing histories by recording all openings and

closings of the medication container. The eMUM company's vision is to see that patients take their medication and it was designed to journey with the patient from day to day and form a simple part of the control and treatment solution to improve health.

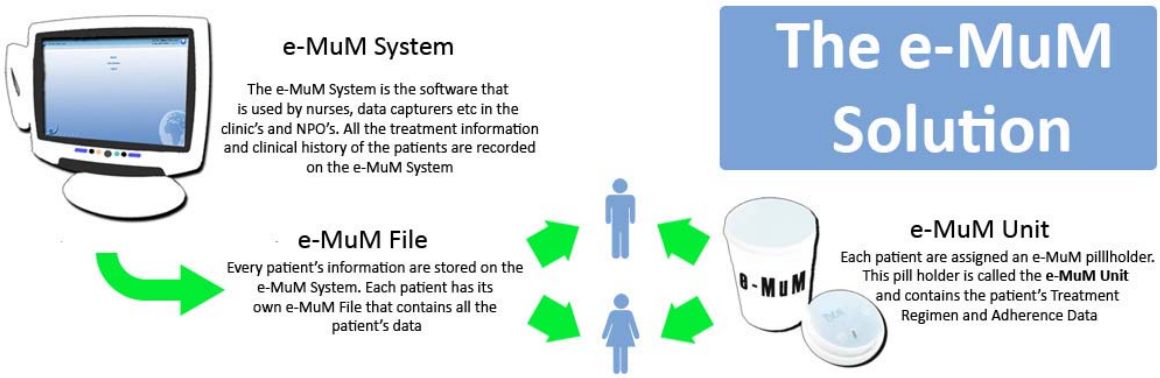


Figure 1: The eMUM solution (eMUM, 2012).

Meyer, Engelbrecht and Summers (2012) conducted an eight month four phase, prospective, experimental study to evaluate the eMUM system for practicality and effect on ART adherence. When they compared adherence monitored with eMUM with adherence according to patient self-report, the patient over-estimated their adherence. It was reported that patient adherence and CD4 count increased and Viral Load decreased in both test (eMUM) and control (no eMUM) arms. It was recommended that eMUM be used to increase adherence when patients start on ART.

1.11 Other methods of adherence monitoring

Patient self-report is often exacerbated and has inherent bias in its measurement, but is still the most widely used method. Pill counts at time of clinic visits have inherent bias in its measurement and are subject to patient's possible faulty recall of events (Mills *et al*., 2006). Frequency of refills and drug assay of blood and urine are also used to measure adherence. Modern methods of adherence monitoring include breathalysers (Henry J. Kaiser Family Foundation, 2008)

wireless real time adherence monitoring (Haberer, 2012) and a smart dispenser with high degree of scalability and remote manageability (Pak and Park 2012). Haberer (2012) claims that wireless adherence monitoring is less expensive than viral load and more accurate than CD4 count for detecting treatment failure. An advantage the wireless system has over eMUM is that it detects missed doses straight away, whereas eMUM can only detect it when patient returns to clinic.

1.12 HIV and TB co-infection

South Africa is highly burdened with HIV, with more than 50% of TB patients in South Africa are infected with HIV (World Health Organization, 2012). Because of a decreased number of CD4 lymphocytes, a person infected with HIV is five times more likely to develop active TB disease once infected with TB, compared to a HIV-negative patient (The South African National TB, 2008). This co-infection accelerates the progression of both diseases (Peloquin, 2008, p.1839). Prescribing TB treatment needs careful consideration of the patient's HIV status and concurrent treatment (Table 3).

Table 3: Standardised national ART regimens for adults and adolescents (1st line) (Department of Health, 2010).

Patient	ART regimen	Comment
All new patients needing treatment, including pregnant women	TDF + 3TC/FTC + EFV/NVP	For TB co-infection EFV is preferred. For women of child bearing age, not on reliable contraception, NVP is preferred
Currently on d4T based regimen with no side-effects	d4T + 3TC + EFV/NVP	Remain on d4T if well tolerated. Early switch with any toxicity. Substitute TDF if at high risk of toxicity (high BMI, low Haemoglobin, older female)
Contraindication to TDF: renal disease	AZT+ 3TC + EFV/NVP	

Where TDF= Tenofovir; 3TC=Lamivudine; FTC=Emtricitabine; EFV=Efavirenz; NVP=Nevirapine; d4T=Stavudine; AZT=Zidovudine)

It follows that this co-infection causes challenges for prescribers when having to add ART (anti-retroviral therapy) to a patient's TB medication. The patient is at risk of developing IRIS, which is more common in HIV-positive patients that are treated concomitantly for TB and HIV. Side effects and pill burden increase when adding three ART drugs to four anti-TB drugs and antimicrobial prophylaxis. The increased risk of suffering from the same or similar adverse effects greatly increases when taking more than two tablets simultaneously. This is the case when taking anti-TB and anti-HIV medications concurrently (Table 4).

Table 4: Shared side-effects of TB treatment and ART (Meintjes *et al.*, 2012). Where AZT = zidovudine; ddI = didanosine; PIs = protease inhibitors; NVP = nevirapine; EFV = efavirenz; NRTIs = nucleoside reverse transcriptase inhibitors; D4T = stavudine; TDF = tenofovir; RAL= raltegravir.

Side-effects	ART	TB treatment
Nausea	AZT, ddI, PIs	Pyrazinamide, ethionamide
Hepatitis	NVP, EFV, PIs (NRTIs can cause steatohepatitis)	Rifampicin, isoniazid, pyrazinamide and many second-line drugs including quinolones
Peripheral neuropathy	D4T, ddI	Isoniazid, ethionamide, terizidone/cycloserine
Renal impairment	TDF	Aminoglycosides
Rash	NVP, EFV, RAL	Rifampicin, isoniazid, pyrazinamide, ethambutol, streptomycin and many second-line drugs including quinolones
Neuropsychiatric	EFV	Terizidone/cycloserine, quinolones, isoniazid

Treatment may include additional drugs when HIV or TB is a resistant strain and as such the risk and degree of intensity of the side effects will increase. Moreover, adverse events requiring alternative ARV drugs are more frequent in those patients starting ART within four weeks of starting tuberculosis treatment (Torok and Farrar, 2011). Some ART and TB medications have drug-drug interactions and need to be taken apart (Table 5).

Table 5: ART interactions with rifampicin and recommendations for co-administration (Meintjes *et al.*, 2012).

Class	ARV agent	Interaction	Dose of ART drug with rifampicin
NRTIs	All in class	No significant pharmacokinetic interactions	No dose adjustment required.
NNRTIs	EFV	Mild reduction in EFV concentrations. In some patients, EFV concentrations mayincrease.	No dose adjustment required (600 mg nocte).
	NVP	Moderate reduction in NVP concentrations	Use standard dosing, but omit the lead-in dose phase and start 200 mg NVP 12-hourly.
	ETV	Marked reduction in ETV concentrations	Do not prescribe concomitantly.
PIs	LPV/r LPV	plasma concentrations significantly decreased	The preferable strategy is to double the dose of LPV/r to 800/200 mg 12-hourly. Alternatively, add 300 mg ritonavir 12-hourly to standard dose of 2 tablets 12-hourly of LPV/r. There is an increased risk of hepatotoxicity with these strategies. These dose adjustments can be made gradually over 1 – 2 weeks.*
	SQV/ r	SQV concentrations are significantly decreased	400 mg SQV plus 400 mg ritonavir 12-hourly Increased risk of hepatotoxicity**.**
	All other PIs	Marked reduction in PI concentrations	Do not prescribe concomitantly.
InSTI	RAL		Marked reduction in concentrations Double the dose of RAL to 800 mg 12-hourly.

*The double dosing regimen is preferred as it is better tolerated. Dose adjustments should be continued for 2 weeks after rifampicin is stopped.
ART = antiretroviral therapy; ARV = antiretroviral; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; InSTI = Integrase inhibitor (integrase strand transfer inhibitor); EFV = efavirenz; NVP = nevirapine; LPV = lopinavir; LPV/r = lopinavir/ritonavir; SQV = saquinavir; SQV/r = saquinavir/ritonavir; RAL = raltegravir.

Table 6: Dosing of ARVs and rifabutin when prescribed concomitantly (Meintjes *et al.*, 2012).

ARV	ARV dose	Change Rifabutin dose
EFV	None	Increase to 450 mg/day
NVP	None	300 mg/day
ATV o r ritonavir-boosted PIs	None	Decrease to 150 mg every second day

ARV = antiretroviral; EFV = efavirenz; NVP = nevirapine; ATV = atazanavir; PIs = protease inhibitors.

In addition, the most common symptomatic side effect of efavirenz (a first line ART) is a sense of altered mental state which can clearly influence adherence. As a result, health care workers are often reluctant to start ART in patient on TB treatment and may prefer to wait until at least the continuation phase of TB treatment before initiating ART.

1.13 When to start ART in TB co-infected patients

Due to this reluctance by health care workers, a couple of years ago, it made sense to first treat the immediate threat of TB before treating the HIV in a co-infected patient (Snyders, 2009).

However, it is now known that the late initiation of ART in HIV- positive TB patients has contributed to high levels of mortality as proven by three randomized controlled trials:

- Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT) (Abdool Karim *et al*., 2010),
- Cambodian Early versus Late Introduction of Antiretrovirals (CAMELIA) (Blanc *et al*., 2011) and

- A Strategy Study of Immediate Versus Deferred Initiation of Antiretroviral Therapy for AIDS Disease-Free Survival in HIV-Infected Persons Treated for Tuberculosis with CD4<250 (STRIDE) (Havlir *et al*., 2011).

Earlier initiation of ART leads to more rapid restoration of the immune-competence needed to cure the tuberculosis and the enhancement of immune responses to other specific pathogens, thereby reducing the risk of opportunistic infections (Blanc *et al*., 2011).Government's policy to accelerate ART initiation, improve clinical outcome and delay AIDS (acquired immunodeficiency syndrome) disease progression implies that most HIV-infected TB patients (whom are severely immune suppressed) should be initiated on ART (Department of Health, 2011).

As a result treatment guidelines in South Africa changed in 2012. Before 2012 ART treatment only started in a person with TB when their CD4 count reached 350/mm³ or less to follow World Health Organization (WHO) guidelines and start ART in HIV-positive TB patients regardless of CD4count. This is in line with the National Strategic Plan's sub-objective to reduce disability and death resulting from HIV, STI (sexually transmitted infections)'s and TB through universal access to HIV and TB treatment as early treatment of HIV will reduce the risk of TB disease. Past successes that guide this National Strategic Plan include good adherence to TB treatment and ART (Department of Health, 2011).

The Adult clinical trial group's STRIDE study investigated when to start ART in TB patients. The STRIDE study's main objective was to determine whether it is better to start HIV treatment at about the same time as TB treatment (within two weeks), or to only start HIV treatment between 8 and 12 weeks after the initiation of TB treatment. This study only included participants with CD4 counts less than 250 mm^3 and suspected TB infection. They based their conclusions on the number and severity of IRIS cases developing after ART was initiated. It was concluded that immediate treatment is the better option with only a small percentage of patients experiencing IRIS and most of these IRIS cases could be treated out of hospital.

Improved clinical outcomes was only statistically significant in patients with CD4 counts <50 (Havlir *et al*., 2011).

A similar outcome was reported by the CAMELIA study. The study population in this study included patients with CD4 of 200 mm^3 or lower and were randomly assigned to early initiation (within 2 weeks after beginning tuberculosis treatment) or later treatment (8 weeks after TB therapy). Even when the analysis included the patients that were lost to follow up in the fatality numbers, the survival rate was still significantly higher in the earlier ART group (p=0.005). The increase in CD4 and reduction in viral load were the same regardless of study arm at week 50. Two other studies (the SAPIT and COMESEM [The retrospective Multicenter Cohort of Patients with HIV-infection in the Madrid South-Eastern Metropolitan Crown] studies) already showed that starting ART within 8 weeks was beneficial, but the CAMELIA and STRIDE studies reduced the timeline to 2 weeks within starting TB treatment (Blanc *et al*., 2011).

The SAPIT trial randomized patients with CD4<500 into three groups namely

- the earlier (within 4 weeks of starting TB treatment),
- the later integrated-therapy group (within 4 weeks after completion of the intensive phase of TB treatment and
- the sequential-therapy group (within 4 weeks of completion of TB treatment).

The sequential therapy group was halted because of increased mortality (Abdool Karim *et al*., 2010). Meintjes, Maartens and Boulle (2012) criticized the SAPIT trial for enrolling patients with late stage HIV onto the sequential arm as high mortality rates should have been anticipated in patients with CD4 counts under 200 when therapy is delayed for 6-8 months.

Although prescribers now know that IRIS is not a reason to delay the addition of ART to the TB patients prescription, as long as it is anticipated and immediately dealt with, there is still concern that the patient may not be adherent to this increased pill burden, may experience impaired tolerability of the combined multidrug regiments, with drug-drug interactions and overlapping toxicity profiles (Wood, 2008). Prescribers may choose to delay initiating therapy in non-compliant patients on TB treatment until at least the continuation phase of the TB treatment and even longer in patients with high CD4 counts. This may be an explanation why only 48% of active tuberculosis patients with HIV in the world were started on ART in 2011 (WHO, 2012).

In order to address this concern of decreased adherence with increased pill burden, the aim of this pilot study was to evaluate adherence of TB patients before and after starting ART document changes in adherence to TB treatment following the initiation of ART.

2. MATERIALS AND METHODS

2.1 Research design and study population

This was a quasi-experimental study of HIV-positive patients receiving standard first line TB treatment at Witkoppen Clinic (Gauteng, South Africa) and who were eligible to start ART. Adherence pre-and post-intervention (ART initiation) were compared. This design is appropriate for the small study population. Participants were enrolled on the day of TB treatment initiation.

Inclusion criteria included: HIV-positive patients with pulmonary TB aged ≥18 years, willing and able to give informed consent, were enrolled if their CD4 was equal to or more than 50 (as explained in introduction, the benefits of starting ART at CD4<50 cells/mm³ has been proven by STRIDE study), but less or equal to 350 cells/mm³. If their CD4 count was unknown at time of start TB treatment, the patient was invited for participation. Participation continued if CD4 result was ≥50 and ≤350 and stopped if it was not.

The ART regimen consisted mostly of efavirenz, lamivudine and tenofovir while few patients were on stavudine and retrovir instead of tenofovir. A pregnant participant was on nevirapine instead of efavirenz. TB therapy at the Witkoppen Clinic consisted of Rifafour® or Ritib® (depending on government tender) in the intensive phase and Rifinah® in the continuation phase.

The dose for Rifafour® or Ritib® and Rifinah® was calculated as for regimen 1 (Table1) based on the pre-treatment body weight. The patients were instructed to preferably take the TB medication on an empty stomach in the morning, unless the patient experienced nausea as a side effect, in which case the tablets were taken after breakfast.

2.2 Sample size

A sample of 50 subjects was calculated to have 90% power to detect a reduction of at least 10% in adherence (% of prescribed doses, i.e. 30 per month) to TB

medication after starting ART. Here a standard deviation for the difference (change) of 21.1% was used, i.e. √2*(100-40)/4 = √2*(Adherence assumed to range from 40% to 100%)/4. This sample size was also sufficient to detect a reduction of 0.25 in the proportion of compliant patients, i.e. patients who took ≥ 80% of the 30 prescribed doses per month, with a power of at least 90%. Testing was done at the 0.05 level of significance. Sample size calculations were performed using nQuery Advisor software.

2.3 Study procedures

Clinic staff was trained to notify the investigator of xpert (Cepheid Xpert MTB/RIF assay, a rapid TB diagnostic platform) positive patients or clinically diagnosed patients who were starting TB treatment on that day. The investigator or study staff would then inform them about the study. “Study staff” refers to the investigator /candidate, or trained staff employed at the clinic.

Study staff completed a screening checklist to confirm that the inclusion criteria were met and recorded reasons for screening failures (see Appendix A). Eligible patients were handed a letter and asked to sign an informed consent (Appendix B).

All patients with TB were assessed by the clinic nurses per routine schedule and procedures. If eligible for ART, the clinic nurse determined the timing of the initiation of ART. At Witkoppen clinic the participants would normally first attend two adherence counselling sessions before initiation of ART. Biological markers including smear microscopy for monitoring of response to TB treatment, and HIV load and CD4 for monitoring response to ART counts were done by Witkoppen clinic in accordance with the national guidelines. During these visits trained study personnel completed the Participant Adherence Record forms (Appendix D). The training of clinic sisters was done by the principal investigator at start-up meetings and the investigator visited the clinic at regular intervals to ensure all study requirements were fulfilled.

As patients can start ART during any point of their TB treatment, patients who signed informed consent was monitored for adherence from the start of TB treatment until the end of TB treatment (determined as cure, treatment completed for six months, transfer out, default, or death). Adherence before and after the intervention (ART) was thus measured using the 'eMUM' electronic medication measuring tool, pill count and patient self-report. The use of 'eMUM' allowed the monitoring of each dose of TB medication. The 'eMUM' monitoring unit stored patient's medical records and history on the unit, was small enough to fit inside the pill container's lid and is shock and water resistant.

The investigator had access to the patients' medical records to obtain information relevant to the study including history of TB, patient weight, extent of disease, presenting symptoms, viral load, CD4 count, concurrent medications. The investigator or study staff recorded these notes of the patient on the clinic record form (Appendix C&D) and verified or updated this information at the scheduled patient visits.

The investigator followed participants on TherapyEdge® software and could see when they booked in, but was difficult to keep track of participants when TherapyEdge® was offline or participants came for unscheduled visits. TherapyEdge® is a real-time tracking device that is used to check patients in, record their vitals, laboratory results and clinician visits and next scheduled visit. The study participants' files were marked with bright green stickers to alert pharmacy staff to dispense TB medication in securitainers® with eMUM lids (Figure 2).

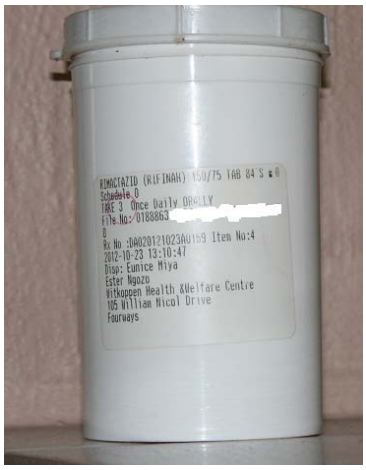


Figure 2: Photo of container given to patients. (The patient's name was taken out for confidentiality).

2.4 Primary endpoint

Primary endpoint: adherence to TB treatment during the month preceding and the month following initiation of ART. This time period was chosen to limit the number of other covariates that may change over time and influence adherence. However, as it cannot be excluded that the effect on adherence would occur at a later time point, the data on adherence to the entire TB treatment episode was collected, but few participants remained on study until completion of TB treatment.

2.5 Adherence calculations

Three methods of adherence calculations were used as detailed below.

2.5.1 eMUM electronic dose monitoring tool

- At enrolment each patient received their TB medication in a securitainer® fitted with an eMUM lid
- The eMUM lid was initiated to contain the patient's data at enrolment
- Participants were counselled at enrolment visit to close lid properly and to bring securitainer® with remaining tablets with at each visit.

- When the patient brought the securitainer® fitted with the eMUM lid back at the subsequent visits, the lid was connected to a computer with the eMUM programme and results could be read as in Figure 3.
- The study team could then confirm that the data on the lid is for the correct patient and received a calendar showing how many times the securitainer® was opened on a specific day if opened at all.
- When participants opened the bottle once or more than once a day, the patient was taken to be adherent on that day.
- When the container was not opened on the day, the patient was taken to be non-adherent on that day.
- In order to be able to compare the pre-and post-ART adherence percentages in the same participant, both the pre-and post-ART data for a particular participant were excluded if either the pre- or post- ART data were not available on the eMUM.



Figure 3: eMUM Adherence screenshot

2.5.2 Patient self-report

At each visit the investigator or study staff completed the CRF for follow up visits (Appendix D).

There are two questions on the follow up CRF that were used to calculate the patient self-report adherence with equation 1:

1. Please ask patient for reasons if eMUM shows tablets were not taken
2. In the last week, have you missed any of your doses?
   If yes, why? {Examples: You went away for the weekend, you forgot, you had too many other thing to take care of, you were feeling sick from something else (e.g. flu, stomach ache) or you were feeling much better}

Patient self-report adherence = (D-DS)/D x 100

Where D = Number of days since last visit

DS = Number of days patient admits to skipping doses

Equation 1: Patient self-reported adherence

2.5.3 Pill count

Pill count adherence was calculated as described in equation 2.

Pill count adherence = (QD-QR)/(D*dd) x 100

Where QD = Quantity dispensed

QR = Quantity returned

D = Number of days since last visit

dd = daily dose (number of tablets)

QD-QR = quantity of anti-TB medication used

Equation 2: Pill count adherence.

2.5.4 Days pre- and post-ART initiation

For all three types of adherence measures the investigator calculated the percentage adherence using the data for the visits that came closest to 28 days pre- and 28 days post-ART initiation. Because the number of days pre- and post-ART initiation varied, adherence was expressed as a percentage.

2.6 Data analysis

The validity and reliability of the various assessment tools were tested with McNemer's test for symmetry with greater than 10% difference indicating a significant difference. The mean adherence of prescribed doses of TB drugs taken pre and post initiation of ART were compared using Student's paired t-test. Descriptive statistics used for data summary were mean and 95% confidence interval for the first adherence measure while frequency, percentage and cross tabulation was used for participants' baseline characteristics. The comparison of age groups with respect to mean adherence was done using a mixed effects model with factors age category(fixed effect), time(random effect: pre versus post within participant) and interaction. Significance testing was done at the $p \leq 0.05$ level for main effects and 0.1 for interaction.

2.7 Ethical considerations

The protocol was approved by the ethics committee (Appendix E) and Witkoppen Clinic (Appendix F). All staff involved in the study received Good Clinical Practice training in the principles of research ethics to ensure that all information was handled in a confidential manner. The database used for analysis was anonymous by giving each participant a unique patient identification number. Access to study-related information was limited to the investigators.

3. RESULTS

3.1 Study population

A total of 83 patients were enrolled between 9 September 2011 to 9 October 2012 (13 months). Fifteen were not eligible and 22 could not be included in the data analysis. (Figure 4).

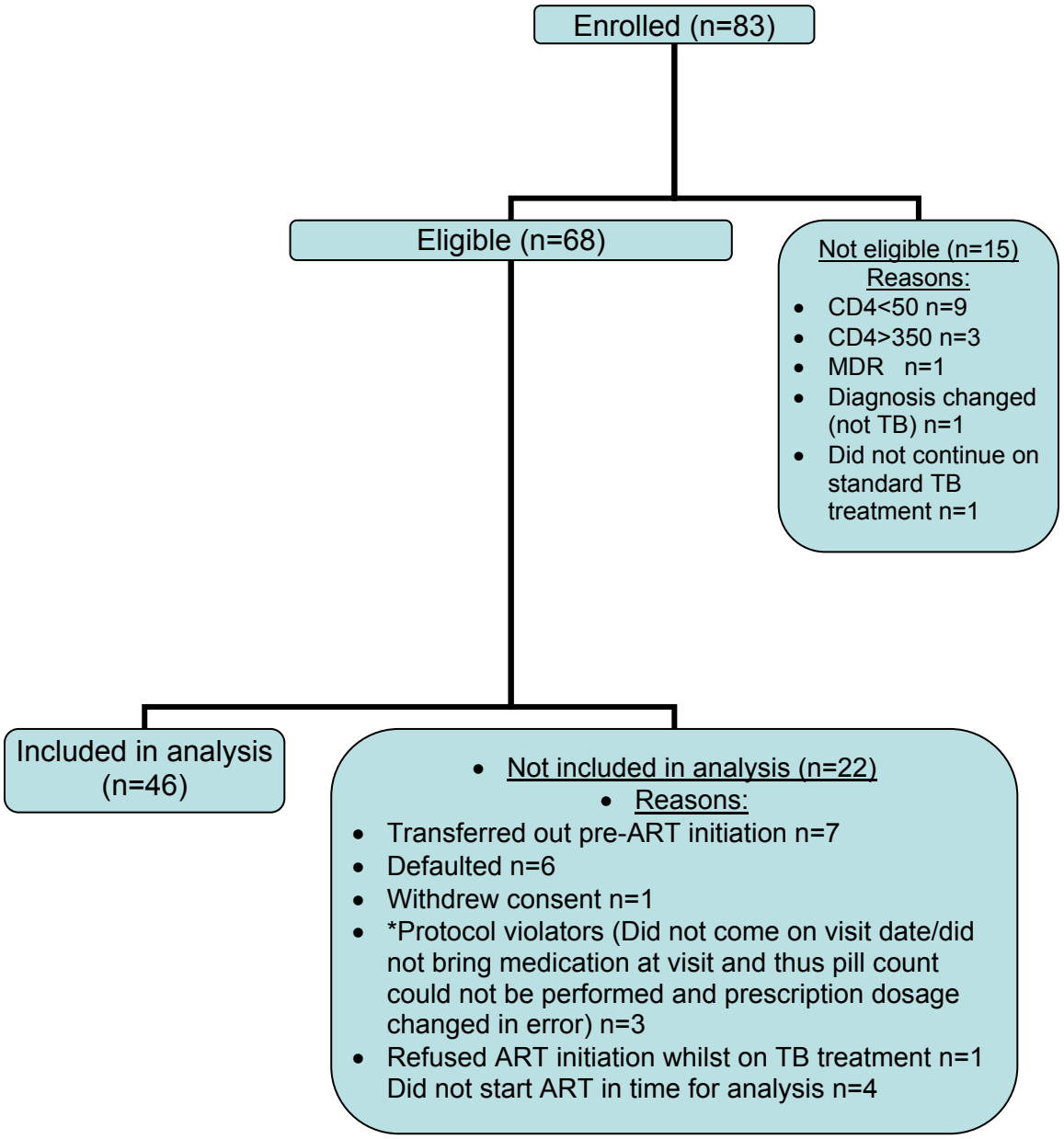


Figure 4: Flow diagram of patients included and excluded in study.

* *Protocol violator 1:* Took wrong dose up to visit 1; forgot returns at home at visit 2 when ARVs were initiated and late for visit 3.

**Protocol violator 2:* Patient was 100% adherent at 1st visit and 76% at visit 2, but it is uncertain if the missed doses were pre- or post-ART or some pre- and some post-ART as the patient came to the clinic between visit 1 and 2 and were not

seen by the study staff. At visit 3 the participant were 87% adherent and 100% adherent at all the subsequent visits.

**Protocol violator 3:* This patient's dosage was changed in error. Patient said she was confused by the fact that her dosage was changed twice and she took medication incorrectly to the extent that according to the analysis her data was an outlier.

The baseline characteristics of the participants included in the analysis are described in the table below.

Table 7: Baseline characteristics of the participants (n=46).

Patient data	Demographics	n	%
Countries of nationality	South Africa	22	48
	Mozambique	3	7
	Zimbabwe	21	46
Gender	Male	25	54
	Female	21	46
Median Age at enrollment	35 years (range 24-59)		
MedianCD4+ T-cell count/mm^3	148 (range 52-344)		
Median Body-mass index	22 (range 16-31)		
Level of education	Illiterate	1	2
	Missing data/Unknown	1	2
	Primary school	3	7
	Primary school completed	1	2
	Secondary school	26	57
	Secondary school completed	14	30
Employed	Yes	20	43
	No	26	57
Average time to start ART since enrollment	33 days (range 9-104)		

Seventeen of the 46 participants included in the analysis were not followed up for the whole six months. Table 8 details the reasons for loss to follow up and the average time these participants were followed.

Table 8: Patient retention.

Reason if not completing 6 months of follow-up	Number of participants	Average time of follow-up (months)
Admitted to hospital (too ill to complete study)	1	3
Deceased	1	1
Defaulted	4	3
Transferred out	3	4
Study end	8	3

3.2 Percentage adherence pre- and post-ART initiation

The pre-and post-ART adherence was assessed using the three methods (Table 9).

Pill count and self-reported adherence data was analyzed for 46 patients, but of these 46 patients only 23 had eMUM data available to analyze. Twenty-three participants' had no eMUM data to analyze due to malfunction of the device as described in section 4.3.1.

Table 9: Mean percentage adherence (95% confidence interval) to TB treatment in the 28 days pre- and post- ART initiation using 3 methods of adherence monitoring

Method of monitoring	Adherence pre ART Mean% (95% CI)	Adherence post ART Mean% (95% CI)	p-value
PILL COUNT (n=46)	97,4 (94,6-100,2)	95,8 (92,9-98,6)	0.30
eMUM (n=23)	65,0 (47,9-82,0)	58,5 (42,7-74,4)	0.36
SELF REPORTED (n=46)	99,9 (99,8-100,08)	99,9 (99.6-100.1)	0.70

By Student's paired t-test the observed data showed that there was no statistical significant difference in adherence before versus after ART initiation, irrespective of the method used to measure adherence ($p>0.05$ for each method).

3.3 Reasons for non-adherence

There were 32 recordings where participants reported missing doses due to the following reasons:

- Distractions (n=2)
  - ❖ When they attended to business
  - ❖ Participant went for medical procedure (sonar)
- Left house without tablets (n=8)
  - ❖ When they go to work or church
  - ❖ When they return home too late
  - ❖ Leave home very early in the morning
  - ❖ Car problems when they were away from home and thus returned home later than planned
- Taking medication as prescribed while not using the eMUM lid

- ❖ Took out more than one dose at a time and kept tablets outside the securitainer® to be taken the next day (n=3)

- Tablets ran out (n=8)
  - ❖ When participants overdosed their medication ran out prior to their visits, but they did not return to the clinic when they noticed they ran out, but waited for their scheduled date
  - ❖ Late for visit
    - ➢ When participants do not return on their scheduled dates their medication ran out
    - ➢ When date was not booked according to quantity of medication that pharmacy dispensed, patients ran out
- Medication side effects
  - ❖ ARV's causing confusion (n=1)
  - ❖ Patient felt nauseous (n=1) Cost
- Some patients reported not having transport money, hence they were late for their visits and asked to be transferred to clinics closer to home.
- Forgetfulness
  - ❖ Participants forgot to take dose at regular time and were not sure if they may still take it later (n=2)
  - ❖ Participant was not sure if dose were already taken or not (n=1)Alcohol abuse
- None of the patients admitted to missing doses due to alcohol abuse and when they were enrolled into the study, no patients confessed to abusing alcohol (n=0)
- Some participants reported that they were not non-adherent, but they suspect that the pharmacy gave them too many tablets (n=2)
- Some participants reported that they took medication every day, but that they took the wrong dose (n=3)

3.4 Relationship between different age groups and adherence

Using a mixed model approach then with respect to pill count adherence percentage, did not differ significantly (p=0.931) and neither did pre- and post-ART (p=0.229). However, at the 0.1 level of significance a significant (p=0.092) interaction between age and time (pre- and post-ART) was detected. In particular this interaction can be ascribed to a sharp decrease post-ART in the age category 31-40 years (Table 10).

Table 10: Relationship between different age groups and adherence as measured by pill count.

Age groups (n)	Mean adherence % pre- ART (95%CI)	Mean adherence % post- ART (95%CI)
21-30 years (12)	95.6 (88.7-102.7)	98.0 (93.3-102.7)
31-40 years (28)	98.4 (95.7-101.0)	93.8 (89.6-97.9)
41-60 years (6)	96.1 (78.7-113.5)	100.8 (98.8-102.8)

3.5 Relationship between CD4 count and adherence

Using a mixed model approach the mean difference between CD4 categories with respect to pill count adherence percentage, did not differ significantly (p=0.414) and neither did pre- and post-ART (p=0.992). However, at the 0.1 level of significance a significant (p=0.063) interaction between CD4 and time (pre- and post-ART) was detected. In particular this interaction can be ascribed to pre-ART in the CD4 category 101-200 mm^3(Table11).

Table 11: Relationship between CD4 count and adherence as measured by pill count.

CD4 at entry (n)	Adherence % before ART (95%CI)	Adherence % after ART (95%CI)
50-100 (n=15)	96.4 (90.7-102.0)	93.9 (86.0-101.8)
101-200 (n=21)	100.0 (97.3-102.7)	98.3 (96.0-100.6)
201-350 (n=10)	93.3 (83.9-102.6)	93.2 (88.0-98.4)

3.6 Relationship between DOT and adherence

Among the 46 participants whose adherence was evaluated pre-ART initiation, 17 were on DOT and 29 were not. After ART-initiation 23 patients were on DOT and 23 patients were not on DOT. Adherence % was calculated using the pill count for 28 days pre- and post-ART (Table 12).

Table 12: Relationship between DOT and adherence as measured by pill count

Participation in DOT	Pre ART initiation Mean (95% Confidence Interval)	P-value	Participation in DOT	Post ART initiation Mean (95% Confidence Interval)	P-value
YES	98.3 (93.7-103.0)	0.62	YES	96.7 (93.8-99.6)	0.54
NO	96.8 (93.1-100.6)		NO	94.9 (90.0-99.9)	

4. DISCUSSION

4.1 Factors that influenced adherence

An overall non-significant difference was found in pill count adherence pre- and post-ART initiation. Further investigation into relationships between adherence and age, CD4 and DOT (Table 10, 11 and 12) also showed non-significant differences.

Nachega *et al*. (2012) investigated the influence of IRIS on ART adherence and the results gave an indication of adherence in patients with low CD4 (median 98). In the South Africa patients enrolled with CD4≤200, the median pill count adherence in the IRIS patients were 95, 5% compared to 98,2% in the patients that did not experience IRIS events. They concluded that possible reasons for the moderately lower, although statistically non-significant (p=0.04), adherence were as a result of morbidity and erosion of patient confidence in ART efficacy in the group that experienced IRIS.

This finding was reconfirmed in 2010 when Nachega *et al*. conducted a study that also found a statistical non-significant high pill count ART adherence in both patients on DOT and non-DOT study arms.

Similarly, it can be concluded from the results of the ART adherence by pill count, that patients on the SAPIT trial that were taking concurrent HIV and TB medication were not affected by the high pill burden as the adherence by pill count was 97.2% and 97.6% in the integrated and sequential treatment arms, respectively (Abdool Karim *et al.,* 2010).

4.2 The different methods used to monitor adherence

Adherence data were collected with eMUM, pill counts and patient self-report. Only pill count data were used in the analysis as eMUM had too many errors

(under-estimated adherence) and patient self-report were found to overestimate adherence (Table 9).

Similarly, the study conducted by Vriesendorp *et al*. (2007) found patient self-report to overestimate and electronic dose monitors to under-estimate adherence and a significant difference between the two. It was reported that in some instances self-reporting were more accurate, while there were also times when electronic monitors were more reliable.

4.3 Challenges encountered by the study

There are several operational challenges of a quasi-experimental study in a complex setting that will be discussed in this chapter.

4.3.1 Adherence monitoring

The eMUM monitor were expected to give objective adherence monitoring data, but showed statistically significant lower adherence than pill count and patient-self report (table 9).

Possible reasons why the 'eMUM' monitoring unit produced discrepant data:

- Only keeps a record of the pill container being opened and not whether or not the correct amount of tablets have been taken or that the tablets were in fact consumed as found by Vriesendorp *et al.* (2007) in their study.
- Calculated poor adherence when participants took out an extra supply to take at a later stage. Vriesendorp's study (2007) also calculated this as non-adherence and justified this by implying that taking out an extra supply is likely to lead to erroneous medication intake. If the participants did not close the lid properly after use, the next opening of the securitainer® was not recorded.
- There was a high turnover of staff in the site pharmacy and the new staff were not familiar with dispensing TB medication in special containers (Figure 5).

The pharmacy staff had to transfer the tablets to bigger securitainers® when more than one month had to be dispensed. The pharmacy staff would sometimes dispense both patients' old securitainer® and normal TB pill box and these patients would then have to be called back by the study staff. This was an inconvenience to all.



Figure 5: Open securitainer® showing anti-TB medication inside.

- Patients that were admitted to hospital received medication from the hospital and their eMUM lid and securitainer® were not returned by the hospital. Depending on where in the follow-up stage these participants were, some of them were followed without further eMUM monitoring. Pill count adherence and patient self-reported adherence data were still collected.
- In some cases the eMUM lid came apart (Figure 6). The manufacturers said it might have been that the securitainers® were too big and caused a suction action on the lid.



Figure 6: Inside the eMUM lid.

- It is battery powered and some units' batteries were flat when patients returned. The participants were unaware of this and the investigator would receive an error message when attempting to read the data on the lid. The units were about 3 years old and it is possible that the expiration date of the batteries had passed. From the 46 patients included in the analysis only half (23) of the participants' eMUM had a reading in the 28 days pre- and post-ART and thus the pill count data were used.
- When the clinic experienced power failures at the clinic (e.g. load shedding), the eMUM could not be read or initiated. It was possible to read the data at the patient's next visit, but could not initiate new patients when there was no power.

4.3.2 Factors affecting patient retention

Many of the patients at Witkoppen clinic are originally from Zimbabwe. Patients that were originally from Zimbabwe, often defaulted as they returned to their homeland. The transport cost of a corpse back to Zimbabwe was reported to be approximately R15, 000. It is thus much cheaper to travel back to the homeland when the participant is still alive and only have to pay the normal taxy/bus rates.

Many of the patients believe in traditional healers (according to their clinic files) and could have defaulted back to their traditional treatments.

Vriesendorp *et. al.* (2007) attributed difficulty in patient retention due to lack of communication systems such as telephone, email or even post in rural areas.

4.3.3 Short follow-up period

The research proposal was to follow the participants for the duration of TB treatment (six months), but very few patients were retained at the clinic for the whole six months and only the conservative 28 days post-ART data could be analysed. This was a similar problem reported by Vriesendorp *et al.* (2007), where they only followed patients for six weeks and collected data on ART adherence. The lack of follow-up was attributed to mortality, hospital admission and lost to follow up, whilst Nachega, et.al. (2012) followed participants for six months and found that participants with IRIS had poorer virological suppression, but the overall ART adherence remained high over the six month period (98,2 and 95,5% in the non-IRIS and IRIS groups respectively).

Nachega, *et al.* (2010) found that ART adherence does not tend to decrease with time, when they compared adherence in DOT and non-DOT patient arms at 6, 12 and 24 months.

4.4 Recommendations

The study highlighted specific reasons that participants were not adherent and snags with using an electronic monitoring system which produced certain recommendations.

4.4.1 Recommendations to facilitate adherence

The following patient counselling scenarios were found to influence adherence of participants on this study.

- The government sometimes do not have stock of Rifinah® 300mg and patients then had to double up on the 150mg. This need to be highlighted to the patient's attention as this was observed to cause confusion.
- The patient needs to understand that the TB medication is taken in the morning and the ART is taken at night as they interact with each other and ART's may cause side effects that are better tolerated while the patient is asleep.
- The patient should be made aware that when ART is initiated he/she might first feel worse before they become better and that this is just because of IRIS and does not mean that the medication is not working.
- The number of tablets and days' supply could be explained to the patient, so that they can realize that something is wrong if they double up and run out.
- Electronic adherence monitoring tools may be helpful to get the patient to admit to non-adherence as it was found that some patients need some probing before admitting to the fact. This could provide the opportunity to discuss possible solutions to the reason for the non-adherence by the patient.

4.4.2 Recommendations for future adherence studies

Unfortunately, with realistic high turnover of staff, a central onsite person needs to oversee that all staff are aware and trained to participate in the study, specifically the pharmacy staff need thorough training on the device to prevent them from giving the patient the medication in a normal box and not in the study container with special lid.

It is a good idea to monitor adherence using more than one method in order to have a backup data collection method. Especially in instances when for example the patient forgets to bring their left over medication to the clinic or gets their medication without the special electronic medication containers or the batteries run down.

Ensure all batteries for the eMUM units are replaced prior to be handed out.
A similar adherence study could be tried in a setting where the turnover of patients is not likely to have such a big influence.

5. CONCLUSIONS

The data from the current study suggests that an increased pill burden of co-treatment of TB and HIV does not lead to reduced adherence to TB treatment. This conclusion is also supported by data from the SAPIT (Abdool Karim *et al.,* 2010) and Nagega (2012) studies.

The fact that this pilot study found a non-significant difference in the change in adherence when pill count pre-and post-ART data were compared, is a significant result which leads to the conclusion that there is no need to do the same study in a larger study population.

Electronic dose monitoring was found to currently being too technically challenging for use in routine clinic setting.

Appendix A: Screening checklist.

Patient ID:

Question	Yes	No
Pulmonary TB diagnosis?		
Standard tablet TB treatment?		
Patient ≥18 years?		
50<CD4<350 cells/mm³ or CD4 count collected but result not yet known		
Patient plans to complete TB treatment at Witkoppen clinic?		
Informed consent signed?		
Alcohol intake (<2drinks/day)		

Completed by:	**Date:**

Appendix B1: INFORMATION LEAFLET AND INFORMED CONSENT

Each participant must receive, read and understand this document before any study-related procedure

STUDY NUMBER: M10925
STUDY TITLE: The influence of ART on adherence to TB treatment in patients using the "eMUM" electronic dose monitoring tool- a pilot study.
SPONSOR: USAID
PRINCIPAL INVESTIGATOR: Marlene Knight
CO-INVESTIGATORS: Liesl Page-Shipp, Annelies Van Rie, Ian Sanne, Jacques De Vos
INSTITUTION: The University of the Witwatersrand
STUDY CONTACT NUMBER: 0827880693

To the Participant: This form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand

INTRODUCTION:
Good day, my name is _____; I am a _____. I would like to invite you to participate in the research study "The influence of ART on adherence to TB treatment in patients using the 'eMUM' electronic dose monitoring tool- a pilot study"'.

Before agreeing to participate, it is important that you read and understand the information leaflet, which explains the study and helps you decide if you would like to participate. If you have any questions, do not hesitate to ask me.

*You may take home **an unsigned copy of this consent** form to think about or discuss with family or friends **before making your decision.***

Participation in a study is voluntary, which means you do not have to participate. You can also stop participating at any time. If you decide not to participate or stop your participation early, this will not affect the care you receive at the clinic.

PURPOSE OF THE STUDY:
You have been diagnosed with TB and HIV. To get cured, you need to take drugs for TB every day for 6 months. You may also need to take drugs for HIV. Taking all these medications every day can be difficult. The purpose of this study is to find out if taking drugs for HIV has an effect on how you take your TB medication.

LENGTH OF THE STUDY AND NUMBER OF PARTICIPANTS:
The study will be performed at Witkoppen Clinic. About 50 adults will participate.
Your participation in this study will be a maximum of 6 months.

PROCEDURES:
If you agree to take part in this study, you will receive your TB medication in a bottle with a cap that records electronically every time you open the bottle. You will be asked to bring your TB medication bottle every time you come to the clinic. We will also ask you a few questions on how easy or difficult it is for you to take your medications. When your CD4 results comes back and shows that your CD4 count is higher than 350 or less than 50, you will not continue taking part in the study.

BENEFITS, RISK, DISCOMFORT OR INCONVENIENCE OF PARTICIPATION
This study involves no risk and no chance of injury.
You will not benefit from participating in the study.
Your participation will help nurses and doctors to better understand the challenges people have when taking drugs for TB and HIV, which may help others like you.

FINANCIAL ARRANGEMENTS:
It will not cost anything to be in this study.
You will not be paid to participate in this study.

CONFIDENTIALITY:
All information will be kept confidential. Only research personnel will have access to the information. The research investigators will not know your name. Reports will not include any information that identifies you as a participant in this study.

ETHICAL APPROVAL
Approval of the study was granted by the University of the Witwatersrand, Human Research Ethics Committee and the Institutional Review Board of the University of North Carolina at Chapel Hill in the US.

ADDITIONAL INFORMATION
If you have questions regarding the study, you can at any time ask me.
If you want any information regarding your right as a research participant, or complaints regarding this research study, you may contact Prof. Cleaton-Jones, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee, which is an independent committee established to help protect the rights of research participants. You can reach him at (011) 717 2301.

WRITTEN INFORMED CONSENT FOR PARTICIPATION:

_____ (Insert name) has provided me with a copy of the informed consent for participation of in the study "The influence of ART on adherence to TB treatment in patients using the 'eMUM' electronic dose monitoring tool- a pilot study" and has fully explained to me the nature, risks, benefits and purpose of the study.

- The study staff has given me the opportunity to ask any questions concerning the study.
- It has been explained to me that I will be free to stop participating in the study at any time, without any disadvantage to future care.
- I have understood everything that has been explained to me and I consent to participate in this study.
- I give permission to collect information from my clinic or hospital file

Printed Name of research participant	**Signature / Mark or Thumbprint**	**Date**

Printed Name of person obtaining permission	**Signature**	**Date and Time**

Appendix B2: INFORMATION LEAFLET AND INFORMED CONSENT (Zulu)

Isingeniso

Sawubona, igama lami ngingu…… ngiyi…….. ngingathanda ukukumema ukuba ube ingxenye yocwaningo " umthelela yama ART ekuphuzeni kahle amaphilisi kubaguli abanesifo sofuba (TB) uma besebenzisa I "eMUM" ubuchwepheshe obusetsheziswayo ukubona ukuthi abantu baphuza kahle yini amaphilisi. – senziwa kwidlanzana labantu".

Nagphambi kokuthi uvume ukuba ingxenye, kusemqoka ukuthi ufunde, bese uyazwisisa iphepha lolwazi, elichaza kabanzi ngesifundo bese likulekelela ukuthi ukhethe ukuba ungathanda yini ukuba ingxenye. Uma unemibuzo ungangabazi ukungibuza.

Ungalithatha uye nalo ekhaya **elingasayindiwe iphepha lesivemelwano elifana naleli** uyocabanga kabanzi noma uyoxoxisana nomndeni wakho noma abangani **ngaphambi kokuba uthathe isinqumo.**

Ukuba ingxeye yalesisifundo kuwukuzikhethela ,okusho ukuthi awuphoqiwe ukuba yingxenye. Ungakwazi nokuyeka noma ingasiphi isikhathi ukuba ingxenye lesesisifundo. Uma unquma ukuyeka ukuba ingxenye yalesisifundo noma uyeka ukubamba iqhaza masishane , lokhu angeke kukuvimbele ukuba uthole ukunakakekelwa emtholampilo.

INHLOSO YALESISIFUNDO

Usutholwe ukuthi une gciwane le TB kanye negciwane lesandulela ngculaza. Ukuze uthole ukwelashwa kumele uthathe amaphilisi e TB zonke izinsuku bizinyanga eziyisithupaha. Kungenzeke kumele uthathe namaphilisi esandulela ngculaza. Ukuthatha lamaphilisi zonke izinsuku kungaba nzima. Inhloso yalesisifundo ukuthola ukuthi uma uthatha amaphilisi esandulela ngculaza kunomthelela yini ekuthatheni amaphilisi egciwane le TB.

UBUDE BESIFUNDO NESIBALO SABANTU ABAZOBAMBA IQHAZA.

Isifundo sizobe senziwa emtholampilo wase Witkoppen. Abantu abawu 50 abazobamba iqhaza. Ukubamba kwakho iqhaza kuzothatha isikhathi esiyizinyanga eziyisithupha.

INDLELA OKUZOKWENZIWA NGAYO

Uma uvuma ukuthatha iqhaza kulesisifundo uzothola amaphilisi akho e TB esebhodleleni elinesivalo esinobuciko bokubona ukuthi liyavulwa ngaso sonke isikhathi. Uzocelwa ukuba uze nalo lelibhodlela lamaphilisi e TB ngaso sonke isikhathi uma uza emtholampilo. Sizokubuza futhi nemibuzo embalwa ngokuthi kulula noma kunzima kangakanani kuwena ukuthatha amaphilisi.

“Uma imiphumela yegazi le CD4 ibuya ikhombisa ukuba ngaphezulu kuka 350 noma ngaphansi 50, angeke usaqhubeka nokubamba iqhaza kulolucwaningo”

INZUZO, UBUNGOZI, UKUNGAPHATHEKI KAHLE NOMA UKUPHAZAMISEKA UMA UBAMBA IQHAZA.

lesisifundo asinabo ubungozi noma ithuba lokuthi ungalimala.

Akukho ozokuzuza ngokubamba iqhaza lesisifundo.

Ukubamba kwakho iqhaza kuzosiza odokotela kanye nabahlengikazi ukuzwisisa kahle izingqinamba abaguli abahlangabezana nazo uma bephuza amaphilisi e TB kanye nawe sandulela ngculaza, okungasiza nabanye abantu abafana nawe.

UHLELO LWEZIMALI

Angeke kukubize lutho ukuba kulesisifundo.

Angeke ukhokhelwe ngokubamba iqhaza kulesisifundo.

IMFIHLO

Yonke imininingwane izobekwa iyimfihlo. Abasebenzi bocwaningo kuphela abazokwazi ukufinyelela lemininingwane. Odokotela bocwaningo angeke balazi igama lakho. Imiphumela angeke ifake noma yini engadalula ukuthi ububambe iqhaza kulesisifundo.

UKUVUMELWA YI ETHICS

Imvume yokwenza lesisifundo yenziwa i University of Witwatesrand, Human Research Ethics Committee kanye ne Institutional Review Board ye University of North Carolina e Chapel Hill e US.

IMININGWANE EYONGEZIWE

Uma unemibuzo mayelana nalesisifundo, ungangibuza noma ingasiphi isikhathi. Uma ufuna imininingwane mayelana namalungelo akho njengo mbabi liqhaza wocwaningo noma unezikhalo mayelana nalolucwaningo, ungathintana no Profesa Cleaton-Jones usihlalo wase University of Witwatersrand, Human Research Ethics

Committee okuyikomidi elizimele elasungulwa ukba lisize ukuvikela amalungelo abantu abathatha iqhaza locwaningo. Ungamthola kule namba (011) 717 2301.

ISIVUMELWANO ESIBHALIWE SOMUNTU OBAMBA IQHAZA.

…….(Faka igama) unginikeze iphepha lesivumelwano sokubamba iqhaza kulesisifundo “umthelela yama ART ekuphuzeni kahle amaphilisi kubaguli abanesifo sofuba (TB) uma besebenzisa I “eMUM” ubuchwepheshe obusetsheziswayo ukubona ukuthi abantu baphuza kahle yini amaphilisi. – senziwa kwidlanzana labantu”.

- Abasebenzi besifundo banginikeze ithuba lokubuza imibuzo mayelana nesifundo.
- Ngichazeliwe ukuthi ngivumelekile ukuyeka ukubamba iqhaza noma inini, angeke ngahlangabezana nankinga yokuthola usizo lokwelashwa esikhathini esizayo.
- Ngizwisise yonke into engichazelwe yona futhi ngiyavuma ukubamba iqhaza kusisifundo.
- Ngiyavuma ukuthi nithathe imininingwane yami emtholampilo noma efayilini lase sibhedlela.

Printed Name of research participant **Signature / Mark or Thumbprint**
Date

Printed Name of person obtaining permission **Signature** **Date and Time**

Appendix C: CRF – For enrolment visit

Patient ID:	Date:
Completed by:	

Question	Yes	No
Does anyone help you to make sure you remember to take your tablets? If yes, give details (e.g. who, how reguarly,…)		
Are you taking any other medications or traditional herbs?		

Age:
Weight:
Height:
Gender:
Address:
Date of TB diagnosis:
Prior TB history:
Presenting symptoms and duration (ask patient about cough, weight loss and fever):
* Cough yes/no for
* Weight loss yes/no for
* Fever yes/no for
Quantity of tablets dispensed:
Return date:

Remember to ask patient to bring container with at every visit!

Appendix D: CRF – For follow up visit

Patient ID:	Date:
Completed by:	

Question	Yes	No
Does anyone help you to make sure you remember to take your tablets? If yes, give details (e.g. who, how reguarly,…)		
In the last week, did your medication make you feel sick? If yes, what was the main complaint?		
In the last week, have you missed any of your doses? If yes, why? {Examples: You went away for the weekend, you forgot, you had too many other thing to take care of, you were feeling sick from something else (e.g. flu, stomach ache) or you were feeling much better}		
Are you taking any other medications or traditional herbs?		

TB Pill Identification Test (PIT)

TB Medication	Knows the name (Y/N)	Knows the number of pills per dose (Y/N)	Time the medication is taken		Knows any additional instruction
			Morning (hour)	Evening (hour)	
				n/a	

Weight:
Presenting symptoms and *duration*:
*** Coughing yes/no**
*** Weight loss yes/no**
*** Fever/night sweats yes/no**
Amount of tablets returned today:
Amount of tablets dispensed today:
Return date:
Please ask patient for reasons if eMUM shows tablets were not taken

APPENDIX E: WITS ETHICS COMMITTEE APPROVAL

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Ms Marlene Knight

CLEARANCE CERTIFICATE	**M10925**
PROJECT	The Influence of ART on Adherence to TB Treatment in Patients using the "eMUM" Electronic Dose Monitoring Tool-A Pilot Study
INVESTIGATORS	Ms Marlene Knight.
DEPARTMENT	Department of Pharmacology
DATE CONSIDERED	01/10/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 01/10/2010 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Robyn van Zyl

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

M Knight
Marlene Knight

Appendix F: Witkoppen Clinic Approval

WITKOPPEN
HEALTH + WELFARE CENTRE

Association Incorporated Under Section 21
Reg. No. 96/00404/08
Non-profit Organisation Reg. No. 001-244NPO
PBO Reg. No. 930009674

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Welfare Centre Fax
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E-mail
info@witkoppen.co.za

28 January 2011

Dear Marlene Knight

AUTHORIZATION FOR RESEARCH STUDY

I hereby grant permission for the study entitled: "**The influence of ART on adherence to TB treatment in patients using the 'eMUM' electronic dose monitoring tool – a pilot study"** to be undertaken at Witkoppen clinic.
I understand that you will perform this study under the supervision of Professor Annelies van Rie and Dr Liesl Page-Shipp.

Yours sincerely

Dr. Jean Basset

Directors
H R Dansey, G Japhet, M Khoza, R Smith, A Christie, L Holding, P Tlabi, J F Bassett (Executive Director), D M Franklin (Chairman)

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