UNIVERSITY OF KWAZULU-NATAL ™

INYUVESI YAKWAZULU-NATALI

"Comparison of Adherence to treatment and effectiveness of Fixed Dose combination ARV drugs to multiple dose regimens in adult patients in public sector"

By

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Submitted as the dissertation component in fulfilment of the requirements for the degree of Master of Pharmacy by research in the school of Health Sciences, University of Kwa-Zulu-Natal

10 August 2018

DECLARATION

I, Ms Helen Lulama Jali-Lubanga, declare as follows:

That the work described in this thesis has not been previously submitted to UKZN or any other tertiary institution for purposes of obtaining an academic qualification, whether by I or any other party.

That my contribution to the project was as follows:

The research proposal was developed following consultations with my supervisor. The proposal was submitted to the Biomedical and Ethics Committee of the University of Kwa- Zulu Natal for review and approval. After receiving ethics approval, I had applied for KZN DOH approval. After receiving KZN DOH approval I organized the data collection with a team of data collectors, under the guidance of my supervisor. I drafted the manuscript presenting the work and this research is my original work. Where the use of the work of others has been made, it has been fully acknowledged.

Signed Date: 10 August 2018

Ms Helen Lulama Jali-Lubanga

Signed Superviso Date: 10 August 2018

Dr Manimbulu Nlooto

DEDICATION

This thesis is dedicated to:

My children, Lonwabo Lubanga and Meleza Lubanga for the sacrifices you made, your understanding, unconditional support and love. I hope this motivates you to achieve the best you can be in life.

My mother, Mrs. Maureen Jali, for your constant motivation and support; your patience and unconditional love.

My colleagues at Uthukela Health District who made all this possible.

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LIST OF ABBREVIATIONS

AIDS – Acquired immunodeficiency syndrome

ADR's- Adverse drug reactions

ART - Antiretroviral treatment

ARV – Antiretroviral

CDC- Centres for Disease control and prevention

CEO's- Chief Executive Officers

CHC – Community Healthcare Centre

DH- District hospital

FDC- Fixed dose combination of Tenofovir/Emtricitabine and Efavirenz.

HAART- Highly active antiretroviral treatment

HCW- health care Workers

HIV – Human Immunodeficiency Virus

ICDM- Integrated Chronic Disease Management

LTF- Lost to follow

NDoH – National Department of Health HCWs

NCDs – Non-communicable diseases PHC

NNRT's- Non Nucleotide Reverse Transcriptase Inhibitors

PDC- proportion of days covered of treatment

PMTCT- Prevention of mother to child transmission

MDC- Multiple dose regimens

MEMS- Medication-monitoring devices

T/O- Transferred out

PHC- Primary Health care

RADUs - Remote Automated Dispensing Units AGL - Adherence Guidelines

tNRTI - Thymidine analogue nucleoside reverse transcriptase inhibitor

RH- Regional Hospital

SA- South Africa

SMS- Short Message service

SPSS - Statistical Package for the Social Sciences

USA- United States of America

VL- Viral Load

WHO – World Health Organisation

Medicines abbreviations

3= Lamivudine, A= Abacavir, E= Efavirenz, F= Emtricitabine, L= Lopinavir, Ritonavir comb,

N= Nevirapine, S= Stavudine, T= Tenofovir, Z= Zidovudine

Atripla – generic for Tenofovir/Emtricitabine and Efavirenz

ABSTRACT

Background

As antiretroviral medicines have become increasingly available and affordable for the treatment of HIV infected patients in South Africa, the adoption of a fixed dose combination (FDC) was implemented in 2013 as a strategy to improve adherence and to ensure that the emergence of resistant strains is delayed. Previous studies in other countries have shown that even with FDC, adherence was still below optimal levels. This study aimed to evaluate the impact of introducing the FDC regimen (emtricitabine/ efavirenz/ tenofovir) on adherence, virologic response, immunological response, retention to care and death rates compared to multiple dose regimens (MDC).

Methods

An institution based, adult patient retrospective record review was conducted at four facilities rendering ART services at Uthukela District, Kwa-Zulu Natal, for ART naïve patients from January 2013 to December 2013. A total of 800 records were sampled, 400 from each of Tenofovir/emtricitabine/efavirenz FDC and the MDC regimens. Proportion of days covered (PDC) and absolute adherence (PDC≥ 95%) were used as parameters to determine adherence for each of the ART regimens, calculated from pharmacy records over a period of 84 days at 6, 12 and 24 months after initiating treatment . Comparison of viral load (VL) suppression, mean Cd4 count, retention to care and death rates as clinical outcomes ,was done for each group to determine regimen effectiveness.

Results

At 0-6 months, 85 patients switched from MDC to FDC, at 12 months 220 had switched, and at 24 months 252 had switched (MDC unswitched). Mean PDC at 6, 12 and 24 months for FDC was (66± 30.29; 60± 34.27 and 54± 36.98days), for the MDC-switched Group was (74±20.14; 70± 27.58 and 65± 33.59 days out of 84 days); and for MDC-unswitched was (59±36.85; 34±39.96 and 22±36.99 days), the difference between FDC and MDC-switched was significant, p value< 0.05, and significant between FDC and MDC-unswitched, p value < 0.05. Absolute adherence for FDC was (65,6%, 59.05% and 50.9%), MDC-switched (73.8%, 72.9% and 71.1%) and MDC-unswitched (64.% 36.4% and 23.3%), at 6, 12 and 24 months. Females on FDC had higher PDC and Absolute adherence than males at 12 and 24 months. VL suppression for FDC was [97%(249 out of 256 tests), 86.2%(145/167), 89.3%(191/124)], for MDC-unswitched [81.8% (23/27), 82%(89/102) ,56%(153/181], p value<0.05, and for MDC-switched [85.5% (23/27); 87.3% (89/102) , 84.5% (153/181)], p value>0.05 compared to FDC, at 6, 12 and 24 months respectively.

Patients on FDC, with PDC below 50%, had VL suppression rates above 90% at 6 months, but this could not be sustainable beyond 6 months. On FDC, VL suppression for females was (97%, 78.8% and 80%) versus males (89.16%, 87.18% and 83.05%), the difference was only significant at 6 months, p value <0.05 At 24 months mean Cd4 count for FDC recovered by 152% from baseline, and by 126% for MDC unswitched. Retention to care for FDC was [91.8% (368/400), 91.8% (367/400), 91% (363/4000], for MDC switched [98.8%(84/85), 94.5% (208/220) and 92.5% (233/252)], and for MDC switched [88.6%984/85), 95.5%9208/220), 81% (120/148)] at 6, 12 and 24 months respectively, p value <0.05. At 24 months the death rate for FDC was 4.75% (19/400), that of MDC switched 1.59% (2/252), and MDC unswitched 17.57% (26/148), p value < 0.05 compared to FDC.

Conclusion

The FDC regimen demonstrated better PDC and absolute adherence than the MDC regimen, however the group that switched from MDC to FDC demonstrated superior PDC and absolute adherence than FDC. Absolute adherence rates for all three regimen groups were less than the optimal level of 90%. VL suppression and Cd4 recovery were significantly higher for FDC than the MDC unswitched regimen. Even though females demonstrated higher adherence than males on FDC, there was no significant difference in VL suppression between the two genders. FDC demonstrated retention to care than the MDC regimen group. The implementation of the FDC regimen improved adherence and clinical outcomes for adult patients on ART.

Keywords: Adherence, Fixed Dose Combination, Viral Load suppression, Retention to Care, Death rates, Fixed Dose Combination ART

CHAPTER 1: INTRODUCTION

1.1 Background

As antiretroviral medicines become increasingly available and affordable for the treatment of human immunodeficiency virus (HIV) infected patients in South Africa, adoption of strategies to ensure that emergence of resistant strains of the virus are delayed, remains critical. These strategies have to be adopted to ensure that patients adhere to treatment to optimize the durability of present treatment regimens and to prolong life.

The South African Department of Health in 2012, implemented the use Fixed Dose Combination antiretroviral regimen to improve adherence to treatment, minimize unnecessary drug toxicities for improved clinical outcomes (Khopotso, 2012), to retain patients on life-long therapy, prevent HIV Disease progression and avert Aids related deaths. Fixed-dose combinations (FDC) of ARV drugs are widely being promoted as a first-line regimen in treatment access programs. Additional advantages of using FDCs are reduced pill load, reduction in prescription errors, and easier delivery of treatments.

A study done in Colorado, USA (Langness, et al., 2015) found that the proportion of days covered on a single regimen of PLWH taken once-daily was significantly higher than the proportion of days covered for multi-tablet once-daily regimens or multi-tablet twice-daily regimens. Research in India has shown that a fixed dose combination of generic Tenofovir/Emtricitabine/Efavirenz is effective, able to achieve viral suppression of 96% at 6 months for antiretroviral –naïve and experienced patients, and is safe to use in those with co-morbid conditions (Pujari et al, 2008). A study by Sax e al, 2012, in USA, observed that only 47% of patients achieved a 95% adherence when taking one pill a day. Another study done in the USA showed that non-adherence to Atripla, a fixed dose anti-retroviral combination, similar in composition to one used in South Africa, was as high as 30% (Clay, 2014). *The Adherence Curve Theory* assumes that at the start of therapy patients become motivated to adhere to their treatment, and often times this is supported by strong patient-provider relationship that is often demonstrated at the start of therapy. This motivation plateaus around 21 weeks after which this motivation declines with time as the patient gets better, and the support provided by clinicians also declines (Friedland, 1999).

Contributing factors to low levels of adherence to antiretroviral therapy (ART) in South Africa, include patient related cultural practices including use of traditional medicines, which can be high as 36% (Peltzer, 2008), resulting in increased rate to drop- outs on treatment, increased drug-drug

interactions with ARV's (Muller, 2011), viral resistance and treatment failure (Mills et al, 2005), however use of traditional medicines seems to decline with longer time of ART (Peltzer, 2008). Other challenges linked to low adherence are related to socio-economic status; socio-cultural environment of the patient, and location of public facilities where patients have to travel for long distances to get the intended care. A study conducted in Kwa- Zulu Natal showed that the distance between the health facility and the patients home have a significant contribution to non-adherence, compounded by socio-economic factors that impact on affordability to access transport to visit the clinics(Marconi, 2014).

Long waiting hours and queues before patients can be able to seen by a clinician is a significant challenge in the public sector facilities. Findings of a study done at kwaThema in SA (Melaku A et al, 2016), before the use of FDC, showed that self-report adherence assessments of patients on ART indicated that 82.8% adhered to treatment while 17.2% did not. Females had an adherence of 80.2% compared to that of males which was 69.9%.

A study done in five sites in Johannesburg, south Africa, demonstated that in anti-retroviral therapy (ART) naïve patients that were enrolled between 2000-2010, retention in care was 60%, and mortality was 9%; and that incomplete adherence amongst patients on HAART is linked to greater risk for residual low levels viremia (Keith, 2014). In a retrospective analysis study, rates of drug resistance were found to be lower with a fixed dose combination single tablet anti-retroviral regimen, than with the same drugs taken individually (Bianco et al, 2014).

Rationale for the study

Since the introduction of HAART in the Public sector in South Africa in 2004, only multiple dose regimens have been used, initially based on Stavudine as the main Nucleotide Reverse Transcriptase of choice, and was often changed with Zidovudine (NDOH Anti-retroviral Guidelines, 2004). The implementation of the tenofovir/ emtricitabine/ efavirenz FDC regimens was done through a phased-in approach, initially prioritising pregnant mothers, and those initiated on ART for the first time. This was then followed by those patients with co-morbidities including TB, and later those that were unstable to Stavudine or Zidovudine based regimens and needed switching to Tenofovir based regimens. Some of the clinicians were very reluctant to switch patients considered stable on multiple dose regimens to the fixed dose combination and switching took almost 18 months after the implementation of the guidelines.

At Uthukela District the Lost to follow up rate to first line multiple dose regimens in 2012, prior to implementation of the FDC regimen was as high as 17% on average, ranging between 8% and

28 % at different facilities (Uthukela District health plan, 2013). Following a report from National Core standard assessments at Uthukela District, in March 2014, non-adherence to anti-retroviral treatment in the district of Uthukela was still high, with adherence levels of 68%.

This study was conducted to ascertain whether there were differences in adherence to treatment, in virologic, immunologic response, retention to care and death rates as clinical outcomes between patients on Fixed Dose Combination (FDC) anti-retroviral drugs, and those that remained on multiple dose regimens in the public sector in Uthukela Health District, South Africa.

1.2 Literature Review

1.2.1 Adherence to Anti-retroviral treatment

Medication adherence is defined as the extent to which a patient takes prescribed medication according to the dosage and frequency recommended by the provide (Andrade, 2006).

The number of daily doses taken affects adherence to anti-retroviral treatment (Grierson et al, 2011). Various factors contribute to non- adherence to highly active Anti-Retroviral therapy (HAART). These are Chronicity, complexity of the treatment regimen, tolerance to treatment, concomitant use of other medication, socio-emotional and biological development of the patient, and the health care system (Grierson et al., 2011).

Improving access to virologic monitoring in Resource restrained settings is essential to maximizing HIV treatment outcomes (Hicks, 2013)

1.2.1.1 Factors contributing to non-adherence to HAART

Chronicity of regimens

Nowadays HIV infection is no longer a death sentence, but rather a chronic disease. Patients remain on treatment for a lifetime. However, it has been shown that that after 6 months of treatment adherence generally declines (van Dulmen, 2007). A study by DiMatteo indicated that on average 24.8% of patients on HAART will be non -adherent to treatment and that this rate increases even further to 58% amongst patients with co-presentation of psychiatric disorders and depression (DiMatteo, 2000).

Complexity of regimens

Research on treatment adherence among most patients with chronic diseases suggests that increased complexity of medication regimens is associated with decreased adherence. Regimen complexity refers to the number of doses taken per day, the number of pills per dose, the number

of different medications taken, and the presence of any food-dosing restrictions or requirements (Mayer, 2001).

HAART regimens can, at times, be extremely complex, involving many doses, many pills, and, often, one or more medications taken for other co-morbid conditions. The complexity of HAART regimens sometimes requires patients to alter their eating and sleeping patterns and requires them to change their daily routine. In a Gardel study done in Europe a two drug regimen performed better than a three drug ART regimen in terms of side effects (Cahn et al, 2014). On the African Continent, a study done in Zimbabwe found that only an estimated 34% of patients were able to access care due to long distances to clinics (Campbell et al, 2012). However, some studies done in Sub-Saharan African countries have found that even in poor resource settings, levels of adherence to ART treatment can be higher than the privileged North American countries (Vreeman et al, 2008), and this can be attributed to supportive networks and a stronger sense of collective responsibility that still exists in the African culture (Ware et al, 2009). Earlier studies have always indicated that increased complexity of a treatment regimen is likely to increase likehood of adherence problems and that treatment regimens of more than one medication are associated with lower adherence rates (Deeks et al., 2010). Prescriptions of multiple medications on different medication schedules also have likelihood for non-adherence (Cahn, 2014).

Taking a single tablet in fixed dose combination, reduces the pill burden taken by the patients; simplifies prescribing, dispensing and stock management since the patients takes only one tablet instead of many more in multiple dose regimens (Davies, 2013).

Tolerance to treatment

Regimens that produce immediate negative physical side effects have been proven to be difficult to adhere to. Anti-retroviral are often associated with immediate side effects, for an example Immune Reconstitution Syndrome, Hypersensitivity reactions, Gastro-intestinal disorders, and general body malaise, to name a few, quite early on initiation of treatment, and this usually , if not communicated well to the patients, is often a deterrent to further use of medication (Martin et al, 2005) .

Concomitant use of other medication, including traditional medicines

The use of traditional and complementary medicines in South Africa has been linked to low levels of adherence to HAART. In KwaZulu- Natal, herbal medicines used by HIV infected patients mainly for pain relief, immune boosters, and for stopping diarrhea, were associated with reduced ARV adherence (Peltzer et al, 2008). In a Pretoria setting, patients who use non prescribed

medicines, including over the counter and herbal medicines have a self-reported adherence level of less than ideal 95% (Malangu, 2007).

Taking concomitant traditional medication with HAART may have clinically significant pharmacokinetic drug interactions mostly with protease inhibitors, and Non Nucleotide Reverse Transcriptase Inhibitors (NNRT's) of which Efavirenz one is of; some of the traditional medicines concerned were St. John Wort, Garlic, Cats claw, and African traditional medicinal plants and extracts, such as, Hypoxis hemerocallidea, Sutherandia frutescens, Cyphostemme hildebrandtii, Acacia nilotica, Agauria salicifolia and elaeodendron buchananii (Muller et al, 2011).

Social, Emotional and Biological Development of HIV Infected patients

In general, demographics such as age, gender, religion and educational level, have not been consistent predictors of adherence. However age in children can be quite significant inaffecting adherence, especially in adolescents. Adolescents have a tendency to neglect their medical care to avoid appearing different from their peers. Adolescents are often pre-disposed to higher stress as they might struggle with coping skills with some challenges they will be facing socially. Puberty, as well as some of the ART side effects, are often associated with changes in distribution of fat and muscle mass, which might result in the adolescents having poor self- esteem about themselves causing them to be more stressed, increasing their chances for non- adherence to treatment (Thompson, 2012).

Alcohol Use and use of hazardous substance and drug abuse

A study done recently in South Africa showed that 37% of 1503 patients attending clinics indicated hazardous/ harmful drinking, and 13% indicated having problems with drug abuse; this was linked to poor clinical outcomes and lower Cd4 counts (Kader and Seedat, 2014). Active alcohol and or substance abuse have been identified as predictors of poor adherence (Behrens, 2010).

Access to medication and long waiting times

The health care system has a direct effect on how the patient participates and co-operates with their medical treatment. Primary care provider turnover was associated with bad patient experience, reduced quality and increased mortality (Reddy et al., 2015).

The ease to readily access medication for treatment has a significant impact on adherence. Shorter clinic waiting time contributes to willingness to attend appointment visits, especially for patients

that are working, and are not able to wait for long periods to pick up their medication. Very often patients have to take a full day off work to attend clinics due to long waiting times, which further impacts on their productivity at work, and compromised finances (Komu, 2008)

A recent study conducted in Kwa- Zulu Natal showed that the distance between the health facility and the patients home have a significant contribution to non- adherence, compounded by socio-economic factors that impact on affordability to access transport to visit the clinics(Marconi, 2014).

Health care provider- Patient relationship

Adherence is related to the quality, duration and frequency of interaction between the clinician and the patient. The clinicians friendliness and approachability enhance patient's perception that they are important and cared for, and this improves communication, where the patient is able to verbalize challenges that they might have with adherence, and the techniques they can adopt to improve adherence. Management through partnership with patients and other health care providers were reported as factors contributing to improve adherence (Naidoo, 2011).

Communication of regimen requirements

Educational strategies such as adherence classes or one- to- one counselling have a positive effect on adherence, however, communication without written information has been shown not to be very effective in improving adherence. A combination of educational and behavioral strategies with written information, to aide patient recall is recommended (Vermeer et al, 2008).

Staff shortage and Patient support systems

Patient-to staff ratio has been shown to be a factor impacting on patient adherence (Schneider H et al, 2010). Collaboration between the different health care professionals; doctors, pharmacists, nurses, social workers, dieticians, and other health care workers, to provide patient adherence support enhances better patient care and understanding of the complex factors that contribute to patient non-adherence (Naidoo, 2011).

Drug availability

Medication possession ratio and medication availability have been factors shown to affect and to assess adherence in several pharmaco-epidemiological and pharmacoeconomic studies (Andrade et al, 2006).

1.2.2. Strategies to Enhance Adherence to HAART

Some of the strategies adopted to enhance adherence are to simplify the regimen as much as possible while incorporating the necessary potency Stone, 2001). Stone argues that when HAART regimen is individualised according to the patient's lifestyle, the recommended dosage regimen is easier to adhere to. He suggests that attempts need to be made as far as possible to avoid medications known to commonly cause extremely unpleasant side effects. Proactively managing these side effects, and informing patients thereof minimises the risk of the patient to suddenly stop medication. The patients are then able to identify these side effects and would often approach health care for management. The use of pictograms and photographs of the medications can be very helpful in understanding directions for medication use. The use of pill calendars and pill boxes are useful tools that can be used as reminders. Programmed sms's are now being used, with advancing technology, as almost 70% of the population use a telephone handset. (Stone, 2001)

1.2.3 Safety and Effectiveness

Efficacy and toxicity of Tenofivir/Emtricitabine and Efavirenz Fixed dose combination

In treatment-experienced adults with HIV-1 infection already virologically suppressed with ART, switching to once-daily triple combination therapy with Efavirenz, Emtricitabine and Tenofovir (including the single-tablet regimen ATRIPLA), was found to be effective in maintaining virological suppression and was generally well tolerated up to 96 weeks' duration (Deeks, 2010). In the United States of America Atripla demonstrated advantage over single drugs with respect to lipid and haemolytic parameters and equivalent incidence of renal toxicity, but bone density seemed to decrease (Clay , 2008).

Another study conducted in antiretroviral (ARV)-naive and experienced patients where thymidine analogue nucleoside reverse transcriptase inhibitor [tNRTI] was replaced by Tenofovir Diproxil Fumarate (TDF) in West India, in 2007; results showed that 96% of the patients were virologically suppressed after 6 months of initiation of treatment, but 2.8% of the TDF Fixed dose combination regimen reported grade 3-4 renal toxicity, higher than was expected (Pujari 2008).

Pozniak et al., in 2006, demonstrated that a multiple dose Tenofivir/ Emtricitabine and Efavirenz regimen, versus a Fixed dose combination of Zidovudine/ Lamivudine / Efavirenz, showed better therapeutic outcomes, at 48 weeks , with the multiple dose TDF regimen showing 75% viral suppression, versus the Fixed dose combination that was zidovudine based that showed 62% viral suppression. There was also a significant increase in Cd4 count, 270 vs 237 cells/mm3. This study indicates that taking a fixed dose combination does not necessarily result in improved clinical outcomes, and that the regimen make-up also contributes to clinical outcomes. However an open label non inferiority study conducted in 2006, by Gallant et al, indicated that a fixed dose combination of Tenofovir/Emtricitabine/ Efavirenz showed superior results in viral suppression versus a fixed daily dose of Zidovudine/ Lamivudine and Efavirenz (84% versus 73% respectively). Immunological function was also better with the TDF Fixed dose regimen, with increases in Cd4 count being 190 vs 158 cells/mm3. More patients in the Zidovudine/ Lamivudine group experienced adverse effects than the Tenofivir/ Emtricitabine group (9% vs 4%). This study confirmed the superiority of Fixed dose Tenofivir over a fixed dose Zidovudine regimen.

Emtricitabine versus Lamivudine

The chemical name of emtricitabine is 5-fluoro-1-(2R,5S)-[2(hydroxymethyl)-1,3-oxathiolan-5-yl] cytosine. Emtricitabine is the (-) enantiomer of a thio analogue of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula: (Gallant et al., 2006)

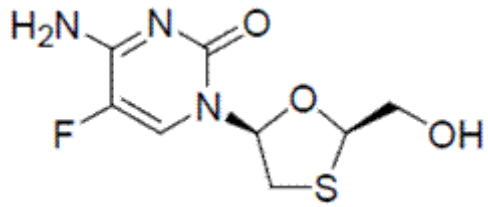

Figure 1.1: Structural formula of Emtricitabine

FTC (Emtricitabine) and 3TC (Lamivudine) are structurally very similar, FTC having just one additional fluorine molecule. In a recent technical update, the World Health Organization (WHO) concluded that 3TC and FTC are clinically and programmatically interchangeable.

Although few direct comparisons have been performed, 3TC and FTC appear to have comparable virological and clinical efficacy and safety. 3TC may rarely be associated with pure red-cell

aplasia, which requires drug substitution, and FTC may occasionally cause palm discolouration, which is usually managed by reassuring patients. Both drugs are active against the hepatitis B virus. Therefore, WHO concludes that 'FTC is an acceptable alternative to 3TC and that 3TC may substitute for FTC or *vice versa*. Both 3TC and FTC can be given as a single daily dose.

1.2.4 Fixed Dose Combinations (FDCs)

1.2.4.1 Formulation of the fixed dose Combination drug

The Fixed dose combination formulation that was on SA government tender was based on generics manufactured by Aspen and Cipla and each ach tablet contains 600 mg of efavirenz, 200 mg of emtricitabine, and 300 mg of tenofovir DF (which is equivalent to 245 mg of tenofovir disoproxil) as active ingredients. The tablets included the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablets are film-coated with a coating material containing black iron oxide, polyethylene glycol, polyvinyl alcohol, red iron oxide, talc, and titanium.

1.2.4.2 Advantages of Fixed Dose Drug Combinations

Regimen and stock management simplification

The use of FDC results in simplified ART prescribing, dispensing and stock management because the number of tablets is reduced when combined to a single tablet (Khapotso, 2013).

Adherence

By reducing the pill burden of the first-line regimen to one pill once daily may improve adherence levels. However, the provision of intensive adherence counselling remains essential (Deek, 2010).

Efficacy

Research has shown that a fixed dose combination of generic Tenofovir/Emtricitabine/Efavirenz is effective, able to achieve viral suppression of 96% at 6 months for ARV –naïve and experienced patients, and is safe to use in those with no co-morbid conditions (Pujari et al, 2008). Other studies showed an advantage of fixed dose combination over those regimens with more complex or frequently administered regimens (Deeks et al, 2010).

1.2.4.3 Disadvantages of Fixed Dose combinations

Disadvantages of fixed drug combinations are often expensive, offer reduced flexibility in dosing, exposure of patients to drugs that they do not need and possibly increasing the risk of adverse side

effects, without increase in therapeutic benefit, and might results in incompatible pharmacokinetics of the individual drugs (Kaplan, 2004).

1.2.5 Multiple Single-Dosage Regimens

1.2.5.1. Definition of a multiple dosage regimen

"Multiple dosage regimens are defined as the manner in which the drug is administered in suitable doses by suitable route, with sufficient frequency that ensures maintenance of plasma concentration within a therapeutic window for entire period of therapy" (Rowland et al, 2014).

Multiple dosing regimens involve taking a number of dosing formulations throughout the day, and taking of individual drugs separately.

1.2.5.2 Advantages of multiple dosage regimens

Advantages of using multiple dose regimens assist in identification of the causal drug when patients experience side effects. Fixed dose combinations and once a day dosing regimens may result in higher peaks of drug concentration reached that might result in toxic doses reached and increased side effects and adverse reactions of the drugs. Giving doses in multiple dose tailored for the drugs half- life, may reduce chances of this happening. With multiple dosing a clinician is able to vary the dose of drug given and allows individualized patient management and flexibility.

1.2.5.3 Disadvantages of multiple dosage regimens

Multiple dose regimens result in higher pill burden for the patients as the patients has to take tablets more frequently and has to take more than one drug, which has implications on increased non-compliance to treatment. It is much more difficult to explain complex regimens to patients thus compromising correct dosing and pill identification.

1.2.6. Theoretical Models

Two models were applicable to the study on adherence to treatment. To assess adherence the Health Belief Model suggests that patients must be involved as partners in their care. The Health Systems Model assists determine some of the factors to be considered that could contribute to optimal clinical care of the patient.

1.2.6.1 The Health Belief Model

The health belief model was developed in the 1950s, and is described as a psychological health behavior change model to explain and predict health-related behaviors, particularly in regard to the uptake of health services (Hochbaun, Rosenstock and Kegels).This model remains one of the

most well-known and widely used theories in health behavior research. The health belief model suggests that people's beliefs about health problems, perceived benefits of action and barriers to action,and self-efficacy explain engagement (or lack of engagement) in health-promoting behavior. More recently, the model has been applied to understand patients' responses to symptoms of disease and compliance with medical regimens (Glanz, 2002).

Table 1.1: Health Belief Theory at a Glance (Glanz et al, 2002, p. 52)

Concept	**Definition**
Perceived Susceptibility	One's opinion of chances of getting a condition
Perceived Severity	One's opinion of how serious a condition is and its consequences
Perceived Benefits	One's belief in the efficacy of the advised action to reduce risk or seriousness of impact
Perceived Barriers	One's opinion of the tangible and psychological costs of the advised action
Cues to Action	Strategies to activate "readiness"
Self-Efficacy	Confidence in one's ability to take action

Although the health belief model attempts to predict health-related behaviors by accounting for individual differences in beliefs and attitudes, it has its limitations in that, it does not account for other factors that influence health behaviors. For instance, habitual health-related behaviors (e.g., smoking) may become relatively independent of conscious health-related decision making processes. Additionally, individuals engage in health-related behaviors for reasons unrelated to health (e.g., exercising for aesthetic reasons). Environmental factors outside an individual's control may prevent engagement in desired behaviors (Glanz, 2002).

1.2.6.2. The Health Systems Model

The Health Systems model seems to be appropriate for addressing some of the environmental factors that have impact on health relate behaviour and health outcomes. Kleiman’s Model of Health Care Systems states that patients and healers exist within a cultural construct, and explains how people in a particular social setting, think about, act in, and use a health care system

(Kleinman, 1980). He proposes that the health system has 3 components: the professional sector that uses methods and materials in healing people; the popular sector, and the Folk (family) sector. The popular sector is comprised of lay, non-specialist persons who depend on the opinions and evaluations of the professional sector. Within the populist sector, are individuals, families, communities, social network and community beliefs. The popular sectors major interest is health maintenance within the community, and community integrity. The model states that the family has influence on how the person seeking health care behaves. Kleinman states that each sector creates its own clinical beliefs and norms associated with sickness, health care seeking behaviour, practitioner-patient relationships, therapeutic activities, and evaluation of outcomes (Kleinman 1980).

Elements of the Health Systems Model

Reddy (2015) argues that, for Professional health system to be functional, Leadership and Governance, Delivery systems accessed by population, funding, drug availability, including widespread availability of anti-retrovirals, laboratory services and a trained workforce, the following elements are necessary for effective service delivery.

Leadership and Governance within the context of the department of Health as stated in South Africa include, evidence based treatment guidelines, partnerships and co –ordination, health, system strengthening, district Health information strengthening, communication and improved referral systems, service delivery improvement, team work and change management for scaling up of services (Mullins, 2007).

1.2.6.3 The Integrated Chronic Disease Management Model (ICDM)

Integrated Chronic Disease Management can be defined as the provision of person-centered care in which health services work with each other and the client to ensure co-ordination, consistency, and continuity of care over time and through the different stages of their condition. This includes coordinated care using a team based, support for self-management approach, regular review and follow up of the patient (Department of Health ICDM Guidelines, 2014).

1.3. Problem Statement and rationale for conducting the research study

In April 2013, the Department of Health introduced a Fixed drug Combination pill, containing Tenofivir 300mg, Emtricitabine, and Efivarenz 600mg, with the purpose of improving cost to Anti-retroviral treatment (ART) and patient adherence to treatment (Davies, 2013) . The FDC regimen introduced was Tenofivir -based, with the one tablet only taken in the evening, while with earlier multi-dose regimens the drugs were taken as single drugs, often taken more frequently.

The GS 99-934 study conducted in USA(Gallant et al, 2006) indicated that a drug combination of single elements of Tenofivir, Emtricitabine and Efivarenz showed superiority over Combivir (Zidovudine/ lamivudine) and Efavirenz combination with viral suppression (84% versus 73%) at 48 weeks, and 75% versus 67% at 96 weeks of therapy. In another study, the ACTG study, 18% of patients on Atripla had 185 Clinical Grade 3 and 4 adverse drug reactions, and 32% laboratory significant adverse effects. In both studies participants discontinued treatment due to intolerance and toxicity to the FDC (Julg, 2008).

Although research has shown evidence of better adherence to fixed dose regimens, (Kling J, 2014) in management of Chronic Obstructive Pulmonary Disease, and in hypertensive patients (Gupta et al, 2010), very few studies have been conducted in South Africa to measure adherence on fixed dose combinations (FDCs) compared to those on multiple dose regimens; and whether fixed dose regimens are safer and show better therapeutic outcomes than the multi-dose regimens. There is a need for monitoring of adherence for a treatment programme as it provides the health providers with an opportunity to identify non-adherence and structure constructive interventions to mitigate and to re-enforce adherence. Another reason why adherence is important in HAART is that even though the patient may show signs of being physically well, indicated by improving Cd4 counts, there is a chance that, if there is interruption in treatment, there could be ongoing viral replication because of mutant viruses that could emerge, which could be not as destructive as the wild type, but would still cause eventual decline in patient survival (Steele, 2007). Patients on multiple-dose regimens are often non- adherent to treatment, resulting in poor clinical outcomes indicated by clinical presentation of Opportunistic Infections, whist on treatment, and poor virological suppression (Ajose O, 2012). However a meta-analysis to compare adherence, safety and effectiveness of fixed dose combinations of anti-hypertensive agents to single drugs, found a significant improvement in adherence with no significant beneficial trends in Blood Pressure control and in adverse effects (Gupta et al, in 2010).

This study was conducted to ascertain whether there were differences in adherence to treatment, and in drug regimen effectiveness between patients on Fixed Dose combination Anti-retroviral drugs, and those on multiple dose regimens in the public sector in Uthukela Health District, South Africa.

1.4. Research questions, hypothesis and objectives

1.4.1. Research Questions

The general question of this study was as follows: "Is the Fixed Dose combination anti-retroviral regimen having better adherence and effectiveness than multiple dose regimens in adult patients in public sector?"

Our specific questions were as follows:

- ✓ Will the fixed dose combination formulation and the resultant reduced pill load result in better adherence to ARV treatment than multiple dose regimens?
- ✓ Will the difference in females and male adherence be bridged by the introduction of the fixed dose combination regimen when compared to multiple dose regimens?
- ✓ Do patients on FDCs have better clinical outcomes than those on multiple dose antiretroviral regimens?

1.4.2 Hypothesis

The null hypothesis assumed that there would be a difference in adherence levels, immunologic and clinical outcomes between ARV patients on fixed dose Tenofivir/ Emtricitibine/ Efivarenz combination and those on multiple single-dose regimens.

1.4.3 Aims and Objectives of this study

1.4.3.1 Aim

The aim of the study was to compare adherence to treatment and effectiveness in patients on Fixed Dose combination anti-retroviral drugs to those on multiple dose regimens in adult patients in public sector.

1.4.3.2 Objectives

The specific objectives of this study were:

1. To establish whether the fixed dose combination formulation and the resultant reduced pill load result in better adherence to ARV treatment than multiple dose regimens.
2. To determine if gender was a significant factor in adherence on FDC compared to multiple dose regimens
3. To determine the effect of FDCs on immunological response, viral load suppression and mean Cd4 count for FDC were compared to multiple dose antiretroviral regimens.
4. To compare retention to care rates between FDC and MDC ART regimens
5. To compare death rates between FDC and MDC regimens

1.5 Research Methodology

1.5.1 Study Design

An institution based, retrospective patient record review was conducted at four Health facilities of Uthukela District, Kwa-Zulu Natal, rendering ART services.

1.5.2 Study area and Period

The study was conducted from January 2016 to December 2017 at four health facilities that were rendering comprehensive ART services at Uthukela District, Kwa-Zulu Natal.

1.5.3 Source and study population

Patient record retrospective reviews of adult patients that were ART naïve on initiation of antiretroviral therapy, and presenting with no active opportunistic infections, were conducted. The study subjects were initiated on the 1st line treatment regimen according the South African ART Treatment guidelines (2013). The study subjects were randomly selected from 4 health facilities in the district, stratified to allow one facility from each level of care, to include: 1 Regional hospital,1 district hospital, 1 Community Health Centre, and 1 Primary health care facility (randomly selected from the 4 local municipalities that make up the district.

1.5.4 Study subjects

Study subjects were stratified according to the two groups:

Group 1: Patients initiated on Fixed Dose Combination (FDC) ART regimen; of Tenofivir, Emtricitabine and Efivarenz, taken once a day.

Group 2: Patients initiated on any other multiple- dose ART regimen.

1.5.4 1 Inclusion Criteria and Exclusion Criteria

1.5.4.1.2 Inclusion Criteria

Study subjects were Adult patients (above 18 years of age) who had been on 1st line ARV treatment. Only those patients who were ARV naïve on initiation of ART therapy were included in the study.

1.5.4.1.2 Exclusion Criteria

Patients younger than 18 years

Patients not on antiretroviral therapy

Patients presenting with any other known comorbid condition on initiation (for an example; TB, opportunistic infections, diabetes, and hypertension).

Patients on 2nd line regimens

Pregnant women that would have been exposed to the PMTCT programme before initiation on HAART.

1.5.5 Sampling Procedure

1.5.5.1 Sampling of Facilities

Data was collected from 4 health facilities in the district, one facility at each level of care, to include: 1 Regional hospital,1 district hospital, 1 Community Health Centre, and 1 Primary health care facility randomly selected from the 4 sub-districts using stratified random selection from the 4 local municipalities in the district.

1.5.5.2 Sampling of subjects

Using a formula by Naing et al, a minimum of 328 participants for each regimen group was required to detect at least 10% difference, a power of 80%, and 95% confidence interval. The sample size was estimated by using the formula: $n = P(1-P)(Z-\alpha/2/E)$, where P = total number of clients on treatment, $(Z - \alpha/2)$ = a constant code representing 95 % of confidence [1.96], E = margin of error [+/- 0.05] (Glenn, 1992). An assumption was made to detect at least 10 % (P =

10%) using the above formula. To accommodate for loss to follow up and drop outs 20% was added to the minimum sample size, a maximum of 400 participants per study group was used in this study. A total sample size of 400 patients on Fixed Dose regimen and 400 patients on multiple dose regimens were included in the final assumption of the sample size. A total Sample size of 800 participants formed the cohort for the study. This maximum sample size was divided among the four facilities included in the study. 100 patients were randomly selected from each of the 4 facilities for fixed dose combination and multiple dose regimens, respectively, using the formula (n+×) based on total number of patients per type of regimen in each facility. For example for facility identified as PHC, with 341 patients on multiple dose, the formula n+3 was used for selecting 100 clinical chart records.

1.5.5.3 Recruitment and selection of study Subjects

Study subjects were patients who started ART therapy in January 2013 to December 2013. The subjects were selected from each of the 4 study facilities, and were stratified according to the ARV treatment regimen they have been initiated on. Study subjects should have been on 1st line ART regimen and should have been on treatment for a minimum period of 3 months, and were initially stratified into two groups as follows:.

Group 1: Patients on Fixed Dose ARV combination of Tenofivir, Emtricitabine and Efivarenz, taken once a day.

Group 2: Patients on multiple- dose, 1st line ART regimens.

1.5.6 Data Collection technique and research instruments

1.5.6.1 Data collection to establish differences in adherence between fixed dose combination and multiple dose regimen regimens

Adherence to HAART can be measured by a variety of methods. The most commonly used methods are pill counts, review of pharmacy records and determination of days covered over a prescribed period, self-reporting, and use of such electronic medication-monitoring devices as MEMS.

No single method has been established as the “gold standard” for measuring adherence. All methods have advantages as well as disadvantages. For example, MEMS are advantageous because of the detailed information they provide regarding the patient's pattern of taking medication, the percentage of doses taken, and the accuracy of the timing of doses, but this method is costly.

Proportion of days covered was used in this study as a Quasi objective measure of adherence to treatment, calculated as a ratio of tablets that were in the patients possession compared to the actual number of tablets they should have had over a pre-determined period. For this study this was measured over an 84 day period, using pharmacy dispensing medication collection history. Absolute adherence was determined as PDC ≥ 95%.

Data was collected using the CDC recommendation of Proportion of days to measure adherence (CDC, 2015). This was modified also to capture CD4 count, and Viral Load suppression as clinical markers for adherence. The Adherence tool was adapted to also capture Age, Gender and overall Clinical Outcomes such as Retained to care, Lost to follow up (after 90 days of therapy) and death. Pharmacy refill records were used to identify adherence to diarized drug collections appointment dates. The data from pharmacy records was triangulated with data from clinical chart records as well as from an electronic data information management system, known as 3–Tier. Adherence was measured utilizing dispensing records following one month of treatment and the number of days the patient had missed their appointment. Adherence was measured on level of adherence over the last 84- day period measured at 3 durations of treatment: at 6 months, 12 months and at 24 months. The Level of adherence was done for each of the two study groups.

1.5.6.1.1 Proportion of Days Covered (PDC)

Proportion of days covered (PDC) over the 84 day period was calculated from pharmacy records at 6 months (from the period of 4 months-6months of treatment), at 12 months (from the period of 10 -12 months of treatment) and 24 months (from the period of 22-24 months of treatment) (Nau, 2009).

PDC was calculated as: $\frac{\textit{No of days medication is recorded as taken X 100}}{\textit{Total number of days in study period (84 days)}}$

1.5.6.1.2. Absolute Adherence

A proportion of patients with PDC ≥ 95%, a standard set for anti-retroviral drugs as absolute adherence, was determined for each study group. Comparison of absolute adherence between the study groups was done at different treatment intervals, at 6 months, 12 months and 24 months.

1.5.6.2 Data collection to determine association between Adherence and Gender: (Females and males as sub-groups)

Comparison of adherence between females and males was done for each of the study groups to determine association between adherence and gender, using PDC and Absolute adherence (PDC ≥ 95%) as adherence parameters. The comparison was also done at different time periods (6 months, 12 months and 12 months) between the two genders. Retention in Care was also

determined for each gender, indicated by the number of patients remaining on treatment at 6, 12 and 24 months.

To determine clinical markers at initiation of treatment, the mean baseline Cd4 count was calculated for each study group.

1.5.6.3 Data collection to determine immunological response for each study group.

Patients' clinical Chart records as well as an electronic Tier-dot net patient information system were used as source for clinical information. Viral load, Cd4 count and Clinical outcomes were used as indicators of immunological response for each patient. Laboratory information was used to triangulate data found in clinical records.

1.5.6.3.1 Viral load Suppression

Viral Load suppression was measured at 6 months, 12 months and at 24 months, for each of the study subjects. Viral load count of less than 400 copies per millilitre of blood, was considered as viral load suppression. The Viral Load suppression rate was measured for each of the groups at 6 months, 12 months and 24 months of therapy.

1.5.6.3.2 Change in Cd4 count

Cd4 count was recorded at baseline, 6 months, 12 months and 2 months for each patient and mean Cd4 was calculated for each study group. Change in Cd4 (cells/$mm^{3)}$ was used as a measure of immunological response to treatment.

1.5.6.3.3 Retention to care and death rates as Clinical Outcomes

Clinical health records, Tier-dot net records and treatment adherence support records were used to determine retention to cate and death rates as clinical outcomes for each study subject. These were then tabulated for each study group, the proportion of patients retained in Care, the number and the proportion of patients that died whilst on treatment was determined at 6 months, 12 months and 24 months for each study group, including those lost to follow up, .

1.5.6.4 Project Management

Data was collected retrospectively. Pharmacists and Pharmacist assistants were trained for data collection and extraction of data from the data sources. A data Capturer was employed to capture data onto collation sheets and computers.

1.6 Data Analysis

1.6.1 Statistical Analysis

The data collected was entered into an Excel spreadsheet and analysed using the Statistical Package for the Social Sciences (SPSS Version 25) as recommended by Saunders *et al.* (2003). Data was analysed using descriptive statistics such as frequency and percentages with 95% confidence intervals. Categorical variables were presented as a frequency and percentage, together with tables or graphs. Associations were carried out where applicable using Pearson chi-square tests. A p-value < 0.05 was estimated to be statistically significant. The researcher sourced the services of a statistician for the analysis of data. Services of medical officer were utilized assist with the analysis of laboratory results and Clinical Information. Interpretation was based on quantitative and qualitative data using triangulation.

1.6.2 Validity, reliability and bias

Validity

The researcher established content validity by consulting with the research experts on the representativeness and suitability of data collection tools and questionnaires. Validity was tested during the pilot study and any gaps like unclear instructions were identified and rectified before the main study.

Reliability

Reliability is defined as the degree to which the data collection method will yield consistent findings, similar observations would be made or conclusions reached by other researchers. Saunders *et al.* (2003: 309). The Cronbach's alpha was used to measure internal consistency. To ensure reliability of results, a simple random selection procedure was used to select study subjects from each of the study groups, from the total sample frame of subjects that met the inclusion criteria. The selection process for the study used a random sampling procedure to select health facilities from each of the 4 sub-districts; including urban, semi urban and rural facilities to ensure inclusivity of all patients from different socio economic classes. The data from pharmacy records was triangulated with data on clinical charts as well as from an electronic data information management system, known as 3 tier. Triangulation of information ensured reliability of data. Patients Lost to follow up were verified as such by Community Care Givers visiting the patients homes to ensure that the patients had not died.

Eliminating Bias

To eliminate bias, the data collectors were trained to retrieve consistent, relevant information following predesigned data collection tools (appendices 7 and 8). Data collectors were external members to health care facilities selected for inclusion in the study. The procedure for sampling of health facilities ensured that patients were selected from all 4 levels of care, that is, a primary health care clinic, a community health care centre, a district hospital and a regional hospital. This was to ensure that the information was not biased to one level of care, or to one group of clinicians which might have limited competency in managing the patients compared to another.

1.6.3 Data Management

Information gathered was kept with the utmost confidentiality more so that the patients are HIV positive and needs to be treated with sensitivity. The study data was coded and therefore, not linked to the participant's name. All study data was kept in a secure place and participant's identity was not revealed during the study, and when publishing the results. On completion of the study, the data was destroyed.

1.7 Pilot Study

A pilot study was conducted in one of the hospitals in UThukela District on approval of the research proposal by the ethics committee as well as the facility Chief Executive officers. The same tools that were used in the main study were used to collect data to ascertain the appropriateness of the tools and the validity of the data. A sample of 50 patients was selected from each study group to make a total study sample size of 100 cases.

1.8 Ethical Considerations

The study received ethical approval from the Biomedical Research and Ethics Committee of the University of KwaZulu-Natal under the reference number BE 084/15, as attached as appendix 3. Permission to conduct the study at health facilities and among HCWs was obtained from the Provincial DOH as well as the uThukela health district. All information was kept confidentially using patient codes instead of patient names, and the records were kept in password protected computers. After completion of the study, all data will be kept for 5 years and then destroyed by shredding. All data saved on password protected computer will be deleted.

Permission Letters

The researcher requested authority to conduct research in the public hospitals in UThukela District from the Head of Department, attached as appendices 2 and 3. Letters of consent were received from the hospital CEO's who acted as gatekeepers for individual institutions (Appendices 4).

Covering Information letter

The researcher wrote a covering letter to the gate keepers and health facility managers explaining the procedures and the reasons for undertaking the research. The covering letter was sent out with the questionnaire and the data collection sheet and is attached as Appendix 5.

Confidentiality and Anonymity

The data collection process did not involve access to confidential personal data, including access to data for purposes other than this particular research project without prior consent of subjects. Researchers and assistants were sworn to confidentiality and participants were assured of anonymity and all the information provided was kept in confidence. The study data was coded and therefore, not linked to the participant's name. All study data was kept in a secure place and participant's identity was not revealed during the study and when publishing the results. The data obtained would be stored and ultimately disposed of after 5 years in a manner that would ensure confidentiality of the participants (Trochim 2006:2).

Risks or Discomforts to the Participant

No direct human participants were involved in the study and any health workers engaged in any manner in accessing data during the course of the study were not asked to perform any acts or make statements which might have caused discomfort, or compromise them, diminish their self-esteem or cause them to experience embarrassment or regret. There were no adverse reactions experienced during the course of the study. The only slight discomfort the HCW respondents could have experienced was information provided regarding health systems and standard of practice of care within the department of health. The gate keepers were notified of this in the information letter.

Research-related Injury

There was no injury or anticipated belated injury to the HCW as they did not perform any acts. Therefore there was no compensation offered.

1.9 Dissemination Plan

Results of the study will be shared with the Uthukela with the facility managers and district Management teams through monitoring and evaluation meetings, and quality improvement forums. Information was shared with the research participant on completion of the HWC interview on health systems, on one-to-one basis, and with their operational managers. Any other relevant information pertaining to patient education will be shared with other patients and the community at health imbizos and through Sukuma Sakhe forums which are community structures based, in local municipalities that have representation with all the other government departments, including the department of social development.

1.10 Layout / Structure of the thesis

Chapter 1 outlines the introduction to the topic by providing information on the background as well as a literature review of existing studies regarding this topic. There is a statement of the problem, as well as research questions, the aim and objectives of this study. Information on the study design including, the study area, study design, statistical analysis and an ethics statement is also outlined.

Chapter 2 is the research article which has been prepared according to submission guidelines to the Biomed Central Journal, entitled, "*Comparison of adherence of fixed dose combination ARV drugs to multiple dose regimens in adult patients in public sector, uThukela District: a retrospective patient record review."*

Chapter 3 is the research article which has been prepared according to submission guidelines to the Biomed Central Journal, entitled, "*Impact of fixed dose combination ART drug regimens on viral load suppression and clinical outcomes in a rural setting in South Africa: a retrospective longitudinal study.*"

Chapter 4 is the synthesis and discussion of the significance of the findings of this study relating to adherence measured as proportion of days covered and absolute adherence, for treatment naïve patients on the fixed dose combination ART regimen compared to those taking multiple dose regimens, the effect of switching patients from multiple dose regimens to a fixed dose combination regimen, and the impact of the ART fixed dose combination on viral load suppression and clinical outcomes..

The appendices are attached at end of this thesis.

REFERENCES

1. Andrade S. et al., 2006.*Methods of evaluation of medication adherence and persistence using automated databases.* Pharmcoepidemiol Drug Saf. 2006

2. Ajose O., et al., 2012. *Treatment outcomes of patients on second-line antiretroviral therapy in resource limited settings: a systemic review and meta analysis*. AIDS. 15 May 2012; 26(8): 929-38

3. Bangalore Sripal et al. 2007. *Fixed-Dose Combinations Improve Medication Compliance: A Meta-Analysis.* The American Journal of medicine, 2007, vol. 120, no 8, pp. 713-719

4. Behrens C.2010. *Adherence to HIV Medications: An Evidence-Based Review.* Available at htpp://www.slideshare.net/mobile/ringer21/adherence-to-hiv-medication-an evidencebasedreview. Assessed on 12 August 2015.

5. Bhagwajee A, Govender K. 2011. *Patterns of disclosure and anti-retroviral treatment adherence in a South African mining workplace programme and implications of HIV prevention*. African Journal of Aids Research, Volume10, Issue supl, 2011. Published online: 15 Dec 2011

6. Bianco Jl, 2014. *Do fixed-dosed Anti-retroviral Combinations Reduce the risk of resistance?* AIDS 2014 Nov 13,28:2531

7. Blair JM, Keith H, 2014. *Assessment of HIV Infected Adults in the U.S. Receiving care in 2009.*MMWR Survellaince Summit 2014 June 20; 63:1

8. Cahn P.et al. 2014. *Dual therapy with lipinovir and ritanovir plus lamivudine versus triple therapy with lipinavir and ritanovir plus two nucleotide reverse transcriptase inhibitorsin anti-retroviral therapy naïve adults with hiv-1 infection; 48 week results of the randomised , open label , non-inferiority GARDEL trial*. Lancet Infect Dis.2014nJul 14(7): 572-80, cited by Sax P in Journal watch AIDS Clinical care.

9. Campbell C, et al. 2012. *Building adherence-competent communities: factors promoting children's adherence to anti-retroviral HIV/AIDS treatment in rural Zimbabwe.* Available at www.ncbi.nlm.nih.gov. Assessed on 10 October 2016.

10. CDC, 2015. *Calculating Proportion of days covered for antihypertensivesa nd Antidiabetic Medications: An evaluation Guide for grantees.* Centres for Disease control and prevention. Aug 015.

11. Clay P, et al. 2008. *One Pill, Once Daily: What Clinicians need to know about Atripla*. Ther Clin Risk Management, April 2008: 48(2): 291-302

12. Davies, N. 2013. *Fixed-dose combination for adults accessing antiretroviral therapy* . SAJHIVMED. March 2013, Vol. 14, No. 1

13. Deeks ED, et al. 2010.*Efavirenz/emtricitabine/tenofovir disoproxil fumarate single-tablet regimen (Atripla®): a review of its use in the management of HIV infection*.Drugs. 2010 Dec 3; 70(17):2315-38.

14. Dimatteo R, 2000. *Depression is a risk factor for non-compliance*. *Meta analysis of the effects of anxiety and depression on Patient adherence.* Arch Intern Med. 200; 160; 2101-2107.

15. Departmemt of Health, 2014. *Integrated Chronic Disease Management Guidelines*. Available at htpp://www.health.vic.gov.au/phc/icdm.

16. Friedland G et al., 1999. *Attaining higher goals in HIV treatment: the central importance of adherence*. AIDS 1999

17. Gallant J, DeJesus E. et al. 2006. *Tenofivir DF, emtricitabine and efavirenz versus Zidovudine, lamivudine and efavirenz for HIV*. N Engl J Med 2006; 354:251-260.

18. Gallant J, et al. 2004. *Efficacy and Safety of Tenofivir DF versus Stavudine in combination therapy in anti-retroviral naïve patients: A 3 year randomised trial*. JAMA 2004: 292 (2): 191-202

19. Glenn D. 1992. *Determining sample size*. University of florida

20. Glanz K, et al. 2002. *Health Behaviour and Health education. Theory, research and practice.* San Fransisco: Wiley & sons.

21. Grieson J, Koelmeyer R, et al.2011. *Adherence to antiretroviral therapy: factors independently associated with reported difficulty taking anti-retroviral therapy in a national sample of HIV-positive Australians.* HIV Medicine Vol 12: 562-569

22. Gupta AK et al. 2010. *Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis.* Hypertension AHA 2010, Feb:55 (2): 399-407.

23. Gupta AK et al. 2010. *Improvement of drug adherence using single pill combinations; what is the evidence?* Available at http://www.espacomp.eu. Assessed on 12 August 2016.

24. Health Belief Model: Available at htpp://www. utwente.nl/cw/theorieoverzicht/. Assessed on 12 August 2016.

25. Health Systems Trust, 2014. *The Quantitative Anti-retroviral Adherence Study in Five sites in Kwa-zulu Natal.* Available at http://www.hst.org.za. Assessed on 03 August 2014.

26. Hicks C. 2013. *Resisting Drug Resistance in Resource –constrained Settings.* HIV/AIDS Clinical Care June 10, 2013.

27. Homer L. et al.,2008. *Effect of Highly Active Antiretroviral Therapy on Viral Burden in the Lungs of HIV-Infected Subjects* **.** *The Journal of Infectious Diseases*, Volume 197, Issue 1, 1 January 2008,

28. Homar F, 2012. *Cost analysis of HIV treatment and drug-related adverse events when fixed dose combinations of antiretrovirals were stopped, versus continuation with FDC'.s*. Health Econ Rev, 2012:2;16, Sep 2012

29. Hochbaun G. 2010. *From social psychology to health brhaviour and health education. Amj public health.* 100 (10): 1864

30. DOH. 2014. *Integrated Chronic Disease Management Guidelines*. Available at htpp://www.health.vic.gov.au/phc/icdm.

31. Julg B. 2008. Atripla: *HIV Therapy in One pill.* Ther. Clin Risk Management June 2008

32. Kader R, Seedat S. 2014. *Hazardous and Harmful use of alcohol and/ or other Drugs and Health status Among South African Patients attending HIV Clinics*. AIDS and Behaviour 18.3 : 524-34

33. Kaplan W. 2004. *Fixed Dose Combination as an innovative delivery mechanism. Priority medicines for Europe and the world. A public health approach to innovation.*

34. Keith H. 2014. citing Chow E et al.*Cd4 cell counts rarely Needed in Patients doing well on ART*. HIV Med 2014 Sep 18.

35. Keith H. 2014. *Incomplete Adherence Linked to greater Risk for Residual Low level Viremia.* AIDS 2014 Jan 14; 28:181

36. Khopotso B. 2012. Simplifying Aids *Treatment*. The centre for the study of Aids, Dec 2012, 20:05.

*37.*Khopotsi B. 2013. Fixed Dose combination ARV's: Everything you need to know. SA News

*38.*Kim S-H, Gerver SM, Fidler S, Ward H. *Adherence to antiretroviral therapy in adolescents living with HIV: systematic review and meta-analysis*. *AIDS (London, England)*. 2014;28(13):1945-1956

*39.*Kipp W., et al., 2010. *Gender differences in antiretroviral treatment outcomes of HIV patients in rural Uganda.* AIDS Care, 2010 March; 22(3): 271-8

*40.*Kleinman A.1980. *Patients and Healers in the context of culture: an exploration of the borderland between anthropology, medicine, and psychiatry*. Berkeley: university of California Press.

*41.*Kling J. 2014. *Once daily Combo outperforms Twice daily in COPD*. Available at http://www.medscape.com. American College of physicians, Oct 2014. Assessed on 09 November 2016.

*42.*Komu P, 2008. Knowledge, attitudes and practicesof HIV patients regarding disclosure of HIV results at Betseda Clinic Namibia. Available at http://www.etd.uwc.ac.za/xmlui/bitstream/handle/11394.

*43.*Langness J et al.,, 2014. *Comparison of adherence rates for antiretroviral, blood pressure or mental health medications for HIV positive patients at an academic medical centre outpatient pharmacy*. J Manage Care Spec Pharm. 2014Aug; 20(8): 809-14

*44.*Malangu N. 2007. *Self-reported use of traditional, complementary and over-the-counter medicines by HIV-infected patients on anti-retroviral therapy in Pretoria, South Africa*. Afr.J. Traditional, Complementary and Alternative Medicines.2007; 4 (3): 273-278.

45. Mattar ME, MarkelloJ, Yaffe S, 1975. *Pharmaceutical factors affecting paediatric compliance.* Pediatrics. Jan, 55 91); 101-8

*46.*Marconi V. 2014. *Early Warning Indicators for Virological failure in the Southern African Context.* AWACC Conference 2014.

*47.*Marconi V. 2013. *How early should we start treatment?* Plos Med 103 Dec 10: 31001568

*48.*Marconi Vet al .2008. *Prevalence of HIV-1 drug resistance after failure of a first highly active anti-retroviral therapy regimen in Kwazulu natal. South Africa*. Available at www.reserachgate.net/piblication. Assessed on 15 October 2016.

49. Martin L, William S, DiMatteo R. 2005. *The Challenge of Patient adherence.* Ther Clin Risk Management, Sep 2005: 1 (3) : 189-199.

50. Martinez-Picado J. et al., 2016. *Persistent HIV-1 replication during antiretroviral therapy.* Curr Opin HIV AIDS. 2016 July: 11(4): 417-423

51. Mayer K. 2001. Strategies for optimising adherence to highly active Antiretroviral therapy> Clicical Inf. Diseases Vol 33,Issue 6

52. Melaku A Eyassu, 2016. Adherence to antiretroviral therapy among HIV and AIDS patients at the Kwa-Thema clinic in Gauteng Province, South Africa. African Journal of primary health care & family medicine: 8(2), 1-7, 2016.

53. Mills E. et al., 2005. *African herbal medicines in the treatment of HIV: Hypoxix and Sutherlandia. An overview of evidence and pharmacology*. Nutritional Journal 2005, 4:19

54. Muller A, Kanfer I.2011. *Potential Pharmacokinetic Interactions between anti-retroviral and medicinal plants used as complementary and African traditional medicines.* Biopharmaceutics and Drug Disposition Vol 32, pages 458-470, Nov 2011.

55. Naidoo P.2006. *Barriers to HIV Care and treatment by doctors: A review of the literature*. SA FamPract 2006; 48(2): 55

56. Naing L et al., Practical issues in calculating the sample size for prevalence studies. Arch oro. Sci; 1: 9-14

57. National Department of Health, 2014. *Guidelines for the Use of Anti-retroviral agents in HIV-1 infected Adults and Adolescent*. Available at http://aidsinfo.nih.gov/guideless/html/1/adult-and –adolescent-arv-guidelines/30/adherence, Assessed on 03 August 2016.

58. Nau P. 2009. *Proportion of Days covered as a preferred method of measuring medication adherence*. Pharmacy Quality Alliance. 2009

59. Olisah O. et al., 2010. *Adherence to highly active anti-retroviral therapyin depressed patients with HIV/AIDS attending a Nigerian University teaching hospital clinic*. Afr. J Psychiatry201013:275-279

60. Parry C. 2014. *Hazardous and harmful use of alcohol and / or other drugs and Health status among South African patients Attending HIV clinics.* Aids and Behaviour 18.3 (Mar 2014: 525-34.

61. Pednekar P. et al., 016. A framework for measuring adherence to multiple medications. Http,// doi.org/10.1016/j.jval.2016

62. Peltzer K. et al., 2011. *Alcohol use and problem drinking in South Africa: findings from a National population based survey.* Afr. Psychiatry, 2011.

63. Peltzer K. et al.2008. *Use of traditional, complementary and alternative medicine for HIV patients in KwaZulu, South Africa.* BMC Public Health 2008, 8: 255. Available at http://www.biomedcentral.com/1471-2458/8/255

64. Pozniak A, Gallant J, et al. 2006.*TenofovirDF,Emtricitabine, and Efivarenz versus Fixed dose Zidovudine/ Lamivudine and Efivarenz in Anti-retroviral – Naïve Patients: Virological, Immunological, and Morphologic Changes- a 96 week analysis*. J. Acquired Immunine Defeciency syndrome: 2006; 4395): 535-540.

65. Pujari, S. 2008.*Effectiveness and safety of generic fixed-dose combination of tenofovir/ emtricitabine/ efavirenz in HIV-1-infected patients in Western India.* Medscape journal of medicine 10.8(2008): 196.

66. Reddy A. et al., 2015. *The effect of Primary care provider turnover:a patient experienceof care and ambulatory quality of care*. JAMA Intern. Med.2015

67. Republic of South Africa. Department of Health. 2011. *Human Resources for Health South Africa. HRH Strategy for the Health Sector, 2012 - 2017*. Pretoria: Government Printer.

68. Republic of South Africa. Department of Health.2003. *The National Health Care Act, Act No.61 of 2003*). Pretoria: Government Printer.

69. Rowland 2014. *Textbook of Biopharmaceuticals, concepts and application.* 3rd edition

70. San Lio MM, et al., 2008. *Evaluating adherence to highly active antiretroviral therapy with use of pill counts and viral load measurement in the drug resources enhancement against AIDS and malnutrition program in Mozambique*. Clinical Infectious Diseases, Volume 46, Issue 19. 15 May 2008, pages 1609-1616

71. Sax P. et al., 2017. *Dual antiretroviral therapy for HIV infection*. Expert opinion on drug safety 16 (8), 923-932

72. Sharp, M.2006. *Application for inclusion of efivarenz, emtricitabine and tenofivir disoproxil fumarate Fixed dose Combination tablets* on the WHO Model List of Essential Medicines

73. Shrestha, J. 2010.*Evaluation of access to Primary Health Care. A case study in Yogyakarta, Indonsia.*

74. Simoni J. 2007.*Adherence to Antiretroviral Therapy for Pediatric HIV Infection: A Qualitative Systematic Review with Recommendations for Research and Clinical Management*, November 21, 2006. Published online May 28, 2007 Pediatrics Vol. 119 No. 6 June 1, 2007 p. e1371 - e1383

75. South African Health Review. 2008. Chapter 2: *A perspective on primary health care in South Africa* by Kautzky and Tollman. Durban: Health Systems Trust.

76. South African Guidelines for the Use of Anti-retroviral agents in HIV-1 infected Adults and Adolescent, 2013. Available at http://aidsinfo.nih.gov/guideless/html/1/adult-and – adolescent-arv-guidelines/30/adherence, Assessed on 03 August 2016.

77. Steel G. et al., 2007. *Development of a Multi-Method Tool to measure ART Adherence in Resource –Constrained Settings: The South Africa Experience*. Rational Pharmaceutical Management Plus Program. Management Sciences for Health.

78. Stone VE et al. 2001. *Antiretroviral Regimen Complexity, Self-Reported Adherence, and HIV Patients' Understanding of their regimens: Survey of Women in the HER Study*. Journal of Acquired Immune Deficiency Syndromes: October1, 2001.

79. Stone VE, 2001.*Strategies for Optimizing Adherence to Highly Active Antiretroviral Therapy: Lessons from Research and Clinical Practice*. Oxford Journals, Medicine, Clinical Infectious Diseases, Volume 33, Issue 6, 865-872.

80. Suarez-Garcia I et al.2014. *Compliance with HIV Treatment Guidelines and Its effect on Outcomes*. HIV Med 2014 Feb 15:86

81. Serebruany V. , 2008. *Bleeding risks of combination vs single antiplatelet therapy: a meta-analysis of 18 randomised trials.* Findamental and clinical pharmacology, Vol 22, issue 3. 15 May 2008.

82. Tang KL. et al., 2017. *Measuring medication adherence in patients with incident hypertension: a retrospective cohort study*. BMC Health Services Research. 13 Feb 2017.

83. Thompson M, et al. 2012. *Guidelines for improving entry into and retention in careand anti-retroviral adherence for persons with HIV: evidence-based recommendations from an*

International Association of Physicians in AIDS Care panel. Ann Intern Med, 2012, Jun 5; 156 (11)

84. Trochim, William M.K. 2006. *Philosophy of Research. Research Methods Knowledge Base*. Accessed 10 May 2016

85. uThukela District Health Plan 2013/14. http:/www.kznhealth.gov.za. Accessed on 15 May 2016.

86. Van Dulmen S et al. 2007. *Patients adherence to medical treatment: a review of reviews*. BMC Health Services Research 2007, 7: 55

87. Vreeman R. et al. 2009. *Impact of the Kenya post election crisis on clinic attendance and medication adherence for HIV –infected children in western Kenya*. Available at www.biomedcentral.com/continent/pdf/1752. Assessed on 12 July 2016.

88. Ware N.et al. 2009. *Explaining adherence success in sub-Saharan Africa: An Ethnographic study*.PLos Med. 2009;6

89. WHO .2012. *Pharmacological equivalence and Clinical Interchangeability of Lamivudine and Emtricitabine: A Review of Current Literature*.

In order to assess the impact of introducing a fixed dose combination regimen to improve adherence in South Africa a paper titled, "*Comparison of adherence of fixed dose combination ARV drugs to multiple dose regimens in adult patients in public sector, uThukela District: a retrospective patient record review"* was prepared. The paper presented the results on assessment of proportion of days covered on treatment by patients on a tenofovir/emtricitabine/ efavirenz based fixed dose combination regimen and those on multiple dose regimens. A comparison was also made between females and males. A manuscript has been prepared following the guidelines of BMC Public Health and presented in chapter 2 below.

CHAPTER 2

"Comparison of adherence of fixed dose combination ARV drugs to multiple dose regimens in adult patients in public sector, uThukela District: a retrospective patient record review."

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Abstract

Background

A fixed dose combination (FDC) Antiretroviral therapy regimen was introduced in South Africa, in 2013 to ensure that patients adhere to treatment and remain virally suppressed throughout their life. The aim of the study was to compare adherence between the new FDC regimen, and multiple dose regimens (MDC).The study also sought to find whether the FDC regimen was able to bridge the difference in adherence between males and females as was indicated in earlier studies for patients on MDC.

Methods

An institution based, adult patient retrospective pharmacy record review was conducted at four facilities at uThukela District, Kwa-Zulu Natal. Study subjects were 800 ART naïve patients initiated on treatment from January to December 2013, with 400 randomly selected from each of tenofovir/emtricitabine/efavirenz FDC and MDC regimens groups. Proportion of days covered (PDC) and absolute adherence (PDC≥ 95%) were used as measure of adherence to treatment, calculated over a period of 84 days prior assessment at 6 , 12 and 24 months on treatment.

Results

At 0-6 months 85 patients switched from MDC to FDC, at 12 months a total of 220 had switched, and at 24 months 252 had switched (MDC-unswitched). Mean PDC at 6, 12 and 24 months for FDC group was (66± 30.29; 60± 34.27 and 54± 36.98 days out of 84 days) respectively, for MDC-switched group (74±20.14; 70± 27.58 and 65± 33.59 days); and MDC-unswitched (59±36.85; 34±39.96 and 22±36.99 days), with difference significant with both groups when compared with FDC, p value<0.05. There was no significant difference in absolute adherence between the three groups at 6 months, p value >0.05. At 12 months PDC≥95% for FDC was 59.05% (222/376), MDC-switched 72.9% (159/218) and MDC-unswitched 36.4% (56/154), p value<0.05. At 24 months FDC was 50.9% (189/3710, MDC-switched 71.1% (175/246) and MDC-unswitched 23.3% (28/120), p value<0.05 with FDC. In the FDC group, mean PDC for females was (69±29.95; 64±32.4, and 57±35.14 days) and males (62±32.24; 53±37.25 and 46±39.87 days), p value<0.05 at 12 and 24 months.

Conclusions

The study found that the newly introduced tenofovir/emtricitabine/efavirenz FDC regimen demonstrated higher adherence levels than MDC-unswitched ART regimens at 12 and 24 months. MDC-switched group demonstrated better adherence than FDC. Switching non-treatment naïve patients from a more complex regimen to a simpler FDC regimen resulted in even better adherence than those that were treatment naïve on FDC. FDC did not bridge the gender adherence gap.

Keywords: Fixed Dose combination, Multiple Dose regimens, Adherence, ART regimen switches, Gender and ART adherence

Background

As antiretroviral medicines become increasingly available and affordable for the treatment of human immunodeficiency virus (HIV) infected patients in South Africa, adoption of strategies to ensure that emergence of resistant strains of the virus are delayed, remains critical. These strategies include introduction of Fixed Dose Combination Antiretroviral therapy regimens that have been adopted to ensure that patients adhere to treatment, to optimise durability of present treatment regimens. Research on treatment adherence among most patients with chronic diseases suggests that increased complexity of medication regimens is associated with decreased adherence. Suboptimal adherence to antiretroviral therapy is well known to be the most common cause of virological failure of HAART. Successful treatment of HIV infection/acquired immunodeficiency syndrome (HIV/AIDS) with highly active antiretroviral therapy (HAART) requires that patients maintain nearly perfect adherence to the prescribed regimen (Stone, 2001).

Since the introduction of HAART in the public sector in South Africa in 2004, only multiple dose regimens were used, initially based on Stavudine as the main Nucleotide Reverse Transcriptase of choice, often interchanged with Zidovudine (NDOH Anti-retroviral Guidelines, 2004). Later on Tenofivir based regimens were introduced and Stavudine use reduced to improve ART toxicity profile due to Stavudine. The Fixed Dose Combination that is Tenofivir based was introduced with the purpose of reducing drug toxicities, improving patient adherence and to reduce treatment cost to Anti-retroviral treatment (ART) (Davies, 2013).

The implementation of the new fixed Drug Combination regimen that was introduced in 2013 by the Department of Health is Tenofivir-based, (containing Tenofivir 300mg, Emtricitabine, and Efivarenz 600mg) with the one tablet only taken in the evening, but some of the prescribers delayed the implementation and retained the older treatment guidelines, prescribing multi-dose regimens.

A meta-analysis study done in South Africa (SA) demonstrated the inverse relationship between medication adherence and dosing frequency, with once daily dosing associated with the greatest adherence (Srivastava et al, 2013). A study done in Colorado, USA (Langness et al, 2015) found that PDC on a single regimen of PLWH taken once-daily was significantly higher than PDC for multi-tablet once-daily regimens or multi-tablet twice-daily regimens. At uThukela District the Lost to follow up rate to first line multiple dose regimens in 2012, prior to implementation of the FDC regimen was as high as 17% on average, ranging between 8% and 28 % at different facilities (uThukela District health plan, 2013). Because ART regimens involve taking multiple drugs,

combining these into one pill taken once daily, thus reducing the pill load and reducing the dosing frequency should have desired outcomes of improved adherence (Deeks et al, 2010).

Disadvantages of fixed drug combinations include reduced flexibility in dosing, exposure of patients to drugs that they do not need possible increased risk of adverse side effects, without increase in therapeutic benefit (Serebruany, 2008). Fixed dose combinations and once a day dosing regimens may also result in higher peaks of drug concentration reached that might result in toxic doses reached and increased side effects and adverse reactions of the drugs. These in turn if not monitored may reduce the intended improved adherence.

There are some advantages in using multiple dose regimens, including ease in identification of the causal drug when patients experience side effects. Giving doses in multiple dose tailored for the drugs half- life, may reduce chances of this happening. With multiple dosing a clinician is able to vary the dose of drug given and allows individualized patient management and flexibility. It is also much more difficult to explain complex regimens to patients thus compromising correct dosing and pill identification.

Findings of a study done at kwaThema in SA (Melaku et al.2016), before the use of FDC, showed that self-report adherence assessments of patients on ART indicated that 82.8% adhered to treatment while 17.2% did not. Females had an adherence of 80.2% compared to that of males which was 69.9%.

Research has shown that a fixed dose combination of generic TDF/FTC/EFV is effective and able to achieve viral suppression of 96% at 6 months for ARV –naïve and experienced patients, and that it is safe to use in those with no co-morbid conditions (Pujari et al, 2008). Other studies showed advantage of using fixed dose combination over those regimens with more complex or frequently administered regimens (Deeks et al, 2010). A study in USA by Sax et al. (2012) observed that only 47% of patients achieved a 95% adherence when taking 1 pill a day, versus 41% - 34% taking 2-3 pills a day. It was hoped that introducing the fixed Dose combination, thus reducing the pill burden of the first-line regimen to 1 pill once daily would improve adherence levels.

The Adherence Curve Theory assumes that at the start of therapy patients become motivated to adhere to their treatment, and often times this is supported by strong patient-provider relationship that is often demonstrated at the start of therapy. This motivation plateaus around 21 weeks after which this motivation declines with time as the patient gets better, and the support provided by clinicians also declines (Friedland, 1999). The rationale of conducting the study was to assess if

there was significant difference in adherence between the fixed dose combination ART regimen and the multiple dose regimens. Some of the clinicians were initially reluctant to switch patients that they considered clinically stable on multiple dose regimens and were slow in switching patients to FDC. The study sought to find if there was any rationale to this thought. The study also sought to find whether the introduction of the Fixed Dose combination had any impact on the difference between males and females as was indicated in studies for patients on multiple dose combination regimens.

Methods

Study Design

An institution based, retrospective patient record review was conducted at 4 Health facilities of Uthukela District, Kwa-Zulu Natal.

Study area and Period

The study was conducted from January 2016 to December 2017 at four Health facilities that were rendering comprehensive ART services.

Source and study population

Patient record retrospective reviews of adult patients who were ART naïve on initiation of antiretroviral therapy were conducted. The study subjects were initiated on the 1st line treatment regimen according the South African ART Treatment guidelines (2013). The study subjects were randomly selected from 4 health facilities in the district, stratified to allow one facility from each level of care, to include: 1 Regional hospital (RH),1 district hospital (DH), 1 Community Health Centre (CHC), and 1 Primary health care facility (PHC) randomly selected from the 4 local municipalities that make up the district.

Study subjects were stratified according to the two groups:

Group 1: Patients initiated on Fixed Dose Combination (FDC) ART regimen; of Tenofivir, Emtricitabine and Efivarenz, taken once a day.

Group 2: Patients initiated on any other multiple- dose ART regimen.

Inclusion Criteria

Study subjects were Adult patients (above 18 years of age) who had been on 1st line ARV treatment. Only those patients who were ARV naïve on initiation of ART therapy were included in the study.

Sampling Procedure

Sampling of Facilities

Data was collected from 4 health facilities in the district, one facility at each level of care, to include: 1 Regional hospital,1 district hospital, 1 Community Health Centre, and 1 Primary health care facility randomly selected from the 4 sub-districts using stratified random selection from the 4 local municipalities in the district.

Procedures for selection of Study Subjects

Study subjects were patients who started ART therapy in January 2013 to December 2013. The subjects were selected from each of the 4 study facilities, and were stratified according to the ARV treatment regimen they have been initiated on. Patient files were selected based on start date, and age, selected only patients 18 years and older. Only patients that remained on treatment beyond the first 3 months of treatment were included in the initial cohort. This cohort formed a baseline of 400 patients on FDC and 400 on MDC. Only study subjects on 1st line ART regimen were selected and stratified into two groups as follows:.

Group 1: Patients on Fixed Dose ARV combination of Tenofivir, Emtricitabine and Efivarenz, taken once a day.

Group 2: Patients on multiple- dose, 1st line ART regimens.

Study participants were sampled from a total sample frame of 4357 patients over the same period as the FDC group. One patient on the study later found to be younger than 18 years, and was excluded from the study, leaving a total sample size of 399 patients.

Sample Size

Using a formula by Naing et al, a minimum of 328 participants for each regimen group was required to detect at least 10% difference, a power of 80%, and 95% confidence interval. The sample size was estimated by using the formula: $n = P(1-P)(Z-\alpha/2/E)$, where P = total number of clients on treatment, $(Z - \alpha/2)$ = a constant code representing 95 % of confidence [1.96], E =

margin of error [+/- 0.05] (Glenn, 1992). An assumption was made to detect at least 10 % (P = 10%) using the above formula. To accommodate for loss to follow up and drop outs 20% was added to the minimum sample size, a maximum of 400 participants per study group was used in this study. A total sample size of 400 patients on Fixed Dose regimen and 400 patients on multiple dose regimens were included in the final assumption of the sample size. A total Sample size of 800 participants formed the cohort for the study. This maximum sample size was divided among the four facilities included in the study. 100 patients were randomly selected from each of the 4 facilities for fixed dose combination and multiple dose regimens, respectively, using the formula (n+×) based on total number of patients per type of regimen in each facility. For example for facility identified as PHC, with 341 patients on multiple dose, the formula n+3 was used for selecting 100 clinical chart records.

Data Collection tools and Procedures

Proportion of days covered was used as Quasi Objective measure of adherence to treatment, calculated as a ratio of tablets that were in the patients possession compared to the actual number of tablets they should have had over a certain period. For this study this was measured over an 84 day period, using pharmacy dispensing medication collection history. Absolute adherence was determined as PDC ≥ 95%.

Data was collected using a pretested structured data collection tool administered by 3 trained health care workers. The tool was adapted from CDC (2015) to calculate Proportion of days covered to measure Adherence, and modified to cater for different regimens. Pharmacy refill records were used to identify adherence to diarized drug collections appointment dates. The data from pharmacy records was triangulated with data from clinical chart records as well as from an electronic data information management system, known as 3–Tier. Adherence was measured utilizing dispensing records following one month of treatment and the number of days the patient had missed their appointment. Adherence was measured on level of adherence over the last 84-day period measured at 3 durations of treatment: at 6 months, 12 months and at 24 months. The Level of adherence was done for each of the two study groups. The Clinical Chart records as well as the 3-Tier patient information system as used as source for records on Cd4 count as a clinical marker.

The Adherence tool was adapted to also capture Age, Gender and overall Adherence Outcomes

a) To determine Patient adherence to ART treatment between the two study groups, FDC and MDC

i) Proportion of days covered (PDC) over the 84 day period was calculated from pharmacy records at 6 months (from the period of 4 months-6months of treatment), at 12 months (from the period of 10 -12 months of treatment) and 24 months (from the period of 22-24 months of treatment).

PDC was calculated as: $\frac{\text{No of days medication is recorded as taken X100}}{\text{Total number of days in study period (84 days)}}$

ii)A proportion of patients with PDC > 95% as Absolute adherence, was also determined for each study group.

iii) Comparison of Adherence between the Different treatment duration periods of ART Initiation

b) To determine association between Adherence and Gender: (Females and males as sub-groups)

Association between PDC and Gender, and Absolute adherence (PDC > 95%) was also determined at different time periods (6 months, 12 months and 12 months), and between the two groups.

To determine clinical markers at initiation of treatment, the mean baseline Cd4 count was calculated for each study group.

Data Quality assurance

Data was collected by using a pre-tested tool by trained health care providers. There was continuous supervision to control the data collection procedure. All the data, from each study site, was checked by the principal investigator, for completeness, clarity and consistency. The different sources of data were used for triangulation. Data was intensively cleaned before analysis.

Data processing and analysis

Data was coded and entered into different statistical tools, including Enterprise Miner and SPSS windows version 20 for further analysis. Adherence to HAART was assessed by using Proportion of days covered (PDC) calculated from using Pharmacy refill records and 3-Tier records. Absolute Adherence was measured by working out the number of days covered above 95%. The age was calculated using the median and standard deviation. Bivariate logistic regression was used to check variables associated with the dependent variable. Odd ratios with 95% CI were computed and those variables found to have p-values of < 0.05 were considered significantly associated with the dependent variable. T-tests were used to find evidence of a significant difference between population means. The t-value of 1.968-1.96 was used to determine 95% level of confidence of difference between 2 population means.

Adherence assessment was done from month 4 to month 6 (over a period of 84 days), for month 6, from 10-12 months for month 12, and from 22-24 months for month 24. Those patients that had died were excluded from the total cohort when determining outcomes for a particular period. Triangulation of information from the clinical chart records as well as the electronic 3-Tier record system was used to determine if the patient was still at the facility, and all "transfer outs" were excluded from the study. On calculating adherence, all patients that could be traced by CCG's and found to be still alive were regarded as defaulters and were included in the analysis of adherence, and only the proportion of days covered (PDC) was calculated based on number of days when they possessed medication as a percentage of adherence over the period of review (84 days), at 6, 12 and 24 months respectively. Patients lost to follow up were regarded as defaulters, and these patients were included in the study in the calculation of adherence, assuming zero PDC. If the records on follow up by CCG's showed that the patient had died, the patient was regarded as an exclusion on calculation of adherence.

Ethical Considerations

Ethical clearance was obtained from the ethical review Committee of the University of Kwa-Zulu Natal. Permission was granted by the Provincial Department of Health. Approval was granted by the Uthukela District Director and the CEO's of the Health facilities, and letters of support were provided. Each caregiver and operational manager of the facilities or ART unit was adequately informed about the purpose of the study. Patient information was kept confidentially using patient codes instead of patient names, and the records were kept in password protected computers.

Results

Socio-demographic characteristics of the study subjects

Two groups of patients, on FDC and MDC, were included in this study. At baseline there were 400 participants from each group. The majority of the participants in both groups were females; with 67.5% (270/400) in the FDC group and 59.3% (237/400) in the MDC group .The median age of the FDC group was 33.1 ± 10.3 years while the median age for the MDC group was 32.9 ± 10.1 years.

Between 0 and 24 months of treatment from the MDC group, a total of 252 participants were switched to Fixed Dose Combination regimen and identified as MDC Switched. Multiple Dose group was assessed as two distinct sub-groups, those that switched to FDC and those that did not switch and remained on MDC. The assessment of adherence was conducted comparing the 3 groups: FDC, MDC Switched and MDC Unswitched.

From the total of 400 prescriptions from the Multiple Dose combination group was comprised of 7 % Abacavir based multiple regimens, 5.25% Stavudine, 3.25% Zidovudine and 84.5 % Tenofivir based. These were sampled from a total sample frame of 4357 patients over the same period as the FDC group. Two patients on the FDC group was found at 24 months to have changed to a second line regimen and was excluded from the 24 month assessment.

Clinical Marker at baseline of the study subjects

At baseline, the mean Cd4 count was 181±123.87 cells/ mm3 for FDC (n=356) and 186±127.53 Cd4 cells/mm3 for MDC (n=337), there was no significant difference between the 2 group Mean Cd4 (p value =0.623).

Table 2.1 presents the change in regimen of participants on FDC and MDC groups over time. At the end of 6 months 85 out of 400 participants were changed from the multiple dose regimen to the fixed dose, leaving 315 remaining on the MDC. Between 7 months and 12 months, an additional 135 were further switched to FDC and finally 32 more were switched between 13 and 24 months. There were no changes in the FDC except for two participants who changed to second line.

Table 2.1: Change of regimen of study participants over time

Duration on treatment	**FDC Group (N=400)**		**MDC Group (N=400)**	
	FDC unswitched	**FDC Switched**	**MDC Unswitched**	**MDC Switched**
Baseline	400	Nil	400	Nil
0- 6 months	400	Nil	315	85
7-12 months	400	Nil	180	220
13-24 months	398	2	148	252
Total at 24 months	**398**	**2**	**148**	**252**

Legend: FDC=fixed dose combination, MDC=multiple dose combination regimen

Adherence Assessment

Proportion of Days Covered

Mean Proportion of days Covered for FDC, MDC Unswitched and MDC Switched over time

Table 2.2 represents the Mean Proportion of days covered for FDC, MDC Switched and MDC Unswitched groups at 6, 12 and 24 months calculated over a period of 84 days. Mean PDC was significantly higher for the MDC switched Group than FDC or MDC Unswitched at all 3 intervals, p value < 0.05. Mean PDC for FDC was in turn higher than MDC Unswitched at all 3 intervals on treatment. Mean PDC for all the groups was below the acceptable standard of 95% PDC (equivalent to 80 days). Mean PDC declined over time for all 3 groups, with mean PDC for MDC unswitched being 22 days out of 84 days at 24 months.

Table 2.2: Mean Proportion of days Covered for FDC, MDC Unswitched and MDC Switched over time

Duration of time on Treatment	**Mean PDC for FDC (out of 84 days)**	**Mean PDC for MDC Switched (out of 84 days)**	**p value**	**Mean PDC for MDC Unswitched (out of 84 days)**	**p value**
6 months	66 ± 30.29(n= 377)	74 ±20.14 (n= 84)	0.0213*	59±36.85 (n=292)	0.0095*
12 months	60 ± 34.27(n=376)	70 ± 27.58 (n=218)	0.0006*	34 ± 39.96 (n=154)	<0.0001*
24 months	54 ± 36.98 (n=371)	65 ± 33.59 (n= 246)	<0.0001*	22 ± 35.99 (n=120)	<0.0001*

Legend: PDC=proportion of days covered, FDC=fixed dose combination, MDC=multiple dose combination. * Statistically significant when compared to FDC.

Comparison of Absolute Adherence between FDC, MDC Switched and MDC Unswitched

At 6 months

Table 2.3 presents the Proportion of participants at different levels of adherence for FDC, MDC switched and MDC-unswitched groups. Absolute adherence (PDC≥95%) at 6 months for FDC was 65.5% (247/377), for MDC switched 73.8% (62/84) and MDC-unswitched 64.73% (189/292). The results suggest that participants with PDC ≥95% were not significantly different between the FDC and MDC Switched, p value>0.05 and between FDC and MDC Unswitched

groups, p value > 0.05. At adherence levels ranging from 80-79%, the proportion of participants for FDC was significantly higher than MDC Unswitched (p value < 0.05).

The proportion of participants with PDC less than 50%, on FDC, PDC was 18.9% (68/377), for MDC switched 7.1% (6/84) and MDC unswitched 29% (85/292). The results suggest that the proportion of participants at this low level of adherence was significantly higher for MDC Unswitched than FDC than MDC, p value < 0.05. The proportion of participants for FDC was in turn higher than that of MDC switched, this was statistically significant (p value < 0.05) at this level of adherence.

At 12 months

PDC ≥ 95% for FDC was 59.04% (222/376), for MDC switched was 72.9% (159/218) and MDC unswitched it was 36.4% (56/154). The results suggest the difference between MDC switched and FDC was significant, p value< 0.05. PDC ≥95% was significantly higher for FDC than MDC unswitched, p value < 0.05.

The results suggest that the proportion of participants with PDC less than 50% increased with all three groups at 12 months. The proportion of participants was 25% (94/376) with FDC, 16.1% (35/218) with MDC switched and 58% (90/54) with MDC switched. The differences between these groups were significant, p value < 0.05.

At 24 months

The proportion of participants with PDC ≥ 95% for FDC was 50.94% (189/371), for MDC switched was 72.9% (175/246) and MDC unswitched 23.3% (28/120). The results suggest that the difference between MDC switched and FDC was statistically significant, p value< 0.05. PDC ≥95% was significantly higher for FDC than MDC unswitched, p value < 0.05. For PDC < 50%, the results suggest that the proportion of participants for all three groups at 24 months further increased at 24 months. The proportion of participants at this level of adherence was 33.2% (123/371) with FDC, 21.5% (53/246) with MDC switched and 73.3% (88/120) with MDC switched. The differences between these groups were significant, p value < 0.05.

Table 2.3 Comparison of proportion of days covered to proportion of participants

Table 3: Comparison of Proportion of days coverted to proportion of participants								
6 months								
PDC	FDC	95%CI	MDC Switched	95%CI	p value	MDC Unswitched	95%CI	p value
≥95%	65.50% (n=247)	60.59-70.14	73.81% (n=62)	63.52-82.02	0.1443	64.73% (n=189)	59.09-69.99	0.8336
80-94%	5.57% (n=21)	3.67-8.36	2.38% (n=2)	0.65-8.27	0.2262	2.05% (n=6)	0.94-4.4	0.022
65-79%	9.28% (n=35)	6.75-12.63	15.48% (n=13)	9.28-2.47	0.0929	3.77% (n=11)	2.12-6.62	0.0051
50-64%	1.59% (n=6)	0.73-3.43	1.19% (n=1)	0.21-6.44	0.7871	0.34% (n=1)	0.06-1.91	0.1164
<50%	18.04% (n=68)	14.49-22.24	7.14% (n=6)	3.31-14.72	0.0139	29.11% (n=85)	24.2-34.56	0.0007
N	377		84			292		
T/O	1.5% (n=6)	0.69-3.23	1.18% (n=1)	0.02-6.37	0.8181	0.95% (n=3)	0.32-2.76	0.5157
Died	4.25% % (n=1	2.67-6.7	0% (n=0)	0.00 - 4.32	0.0536	6.35% (n=20)	4.15-9.60	0.2076
Total	400		85			315		
12 months								
PDC	FDC	95%CI	MDC Switched	95%CI	p value	MDC Unswitched	95%CI	p value
≥95%	59.04% (n=222)	54-63.89	72.9% (n=159)	66.68-78.4	0.0007	36.4% (n=56)	29.18-44.2	0.0076
80-94%	5.85% (n=22)	3.89-8.7	3.2% (n=7)	1.56-6.48	0.1498	0.6% (n=1)	0.11-3.59	0.0512
65-79%	8.78% (n=33)	6.32-12.07	6.9% (n=15)	4.21-11.04	0.4122	3.9% (n=6)	1.8-8.24	0.5029
50-64%	1.33% (n=5)	0.57-3.07	0.9% (n=2)	0.25-3.29	0.6527	0.6% (n=1)	0.11-3.59	<0.0001
<50%	25.00% (n=94)	20.89-29.61	16.1% (n=35)	11.78-21.51	0.0108	58.4% (n=90)	50.54-65.93	
N	376		218			154		
T/O	1.5%(n=6)	0.69-3.23	0.91% (n=2)	0.25-3.25	0.5353	1.11% (n=2)	0.3-3.96	0.7114
Died	4.5% (n=18)	2.87-7.00	0% (n=0)	0.0-1.72	0.0001	13.33% (n=24)	9.12-19.07	0.0001
Total	400		220			180		
24 months								
PDC	FDC	95%CI	MDC Switched	95%CI	p value	MDC Unswitched	95%CI	p value
≥95%	50.94% (n=189)	45.87-55.99	71.1% (n=175)	65.19-74.44	<0.0001	23.3% (n=28)	16.66-31.65	<0.0001
80-94%	5.4% (n=20)	3.52-8.18	2.4% (n=6)	1.12-5.22	0.07346	1.7% (n=2)	0.46-5.88	0.08726
65-79%	9.4% (n=35)	6.86-12.83	4.1% (n=10)	2.23-7.33	0.01208	0.8% (n=1)	0.15- 4.56	0.00168
50-64%	1.1% (n=4)	0.42-2.74	0.8% (n=2)	0.22-2.91	0.7414	0.8% (n=1)	0.15 -4.56	0.8181
<50%	33.2% (n=123)	28.55-38.09	21.5% (n=53)	16.86-27.09	0.00174	73.3% (n=88)	64.78-80.43	<0.0001
N	371		246			120		
T/O	2.0% (n=8)	1.02-3.92	1.59% (n=4)	0.62-4.01	0.69654	1.35% (n=2)	0.37-4.79	0.5892
Died	4.75% (n=19)	3.07-7.33	1% (n=2)	0.22-2.84	0.00512	17.57% (n=26)	12.28-24.5	<0.0001
Total	400		252			148		

Comparison of PDC and Absolute Adherence over time between FDC, MDC Switched and MDC Unswitched

Figure 2.1 indicates that in all groups, the proportion of patients with PDC ≥ 95% (Absolute Adherence) reduced with time from 6 months, 12 months to 24 months, with the least reduction noted in the MDC Switched group. At all intervals the proportion of participants with PDC ≥ 95% was higher for MDC Switched group than either FDC or the MDC unswitched groups. The rate of decline in PDC≥ 95% over time was much higher for the MDC Unswitched group.

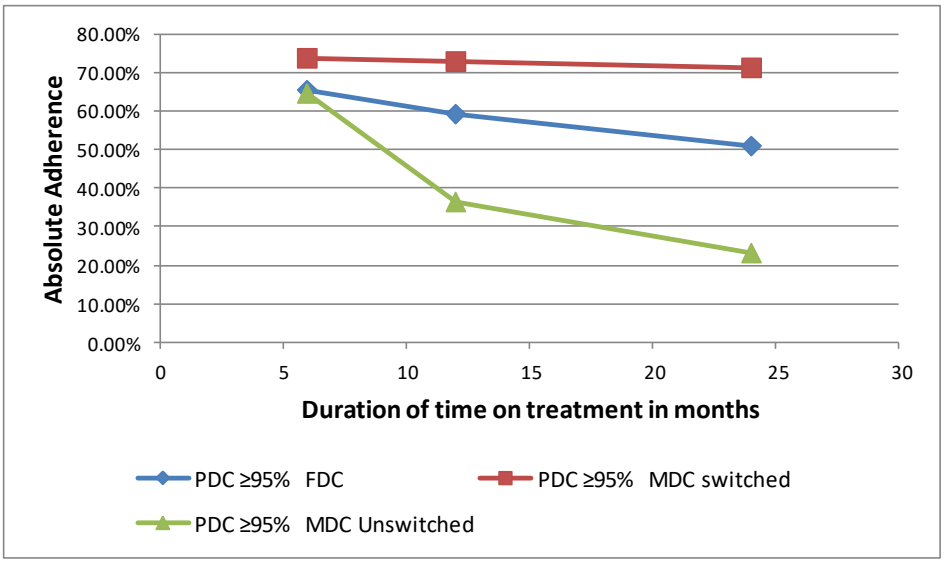

Figure 2.1: Absolute adherence (PDC ≥95%) on FDC, MDC Switched and MDC Unswitched groups over time. Legend: PDC=proportion of days covered, FDC=fixed dose combination, MDC=multiple dose combination regimen

Differences in Proportion of Days Covered between females and males

Table 2.4 presents differences in mean PDC in days, between females and males at months 6, 12 and 24, with FDC, MDC Switched and MDC Unswitched groups. In the FDC group, mean PDC for females was (69±29.95; 64±32.4, and 57±35.14 days) and males (62±32.24; 53±37.25 and 46±39.87 days). The results suggest that for the FDC group, mean PDC for females was higher than that of males, but was only statistically significant at 12 and 24 months, p value< 0.05. In the MDC Switched group, males had a mean PDC higher than that of females, but at 12 and 24 months females had a higher mean PDC, but the difference was not statistically significant, p value >0.05. Again, mean PDC for males in the unswitched group was higher than that of females at 6, 12 and 24 months; however the difference was not statistically significant, p value > 0.05.

Table 2.4 suggests that with both genders in the three groups, Mean PDC declined with time.

Table 2.4: Differences in mean PDC amongst females and males

Legend: PDC=proportion of days covered, FDC=fixed dose combination, MDC=multiple dose combination regimen.*statistically significant between the two genders

Duration on Treatment in months	Means of PDC with FDC out of 84 days		p-value	Means of PDC with MDC Switched out of 84 days		p-value	Means of PDC with MDC Unswitched out of 84 days		p-value
	Females	Males		Females	Males		Females	Males	
6	68±29.25 (n=259)	62±32.24 (n=118)	0.9353	72±22.87 (n=58)	79±10.96 (n=26)	0.1462	57±37.9 (n=166)	62±35.34 (n=126)	0.2944
12	64±32.40 (n=259)	53±37.25 (n=117)	**0.0068***	71±27.16 (n=135)	68±28.29 (n=83)	0.3907	31±39 (n=98)	38±40.73 (n=77)	0.255
24	57 ± 35.14 (n=256)	46 ± 39.87 (n=115)	**0.0067***	66 ± 32.79 (n=147)	63 ± 34.85 (n=99)	0.5067	20 ± 34.62 (n=71)	25 ± 38.02 (n=49)	0.4218

Differences in Absolute Adherence between Females and Males

Table 2.5 presents differences in Proportion of Absolute Adherence between females and males for the 3 study groups at months 6, 12 and 24 months. The results suggest that the proportion of participants with Absolute Adherence (PDC ≥95%) was significantly higher for females than males on the FDC regimen at 6 and 12 months (68.3% vs 59.3%, and 62.5% vs 51.3 % respectively), p value< 0.05. No significant difference was noted between the two genders at 24 months. The proportion of participants with Absolute Adherence was higher for females than males on the MDC Switched regimen at 12 and 24 months, the difference between the two genders was not statistically significant, p value> 0.05. Absolute adherence at 6 months for males in the MDC Unswitched group was significantly higher than that of females, p value < 0.05; however at 12 and 24 months for this group there was no significant difference noted in absolute adherence between the two genders.

Table 2.5: Differences in proportion of Absolute Adherence (PDC≥95%) between females and males

Duration on Treatment	Absolute Adherence (PDC ≥95%) proportions on FDC				p-value	Absolute Adherence (PDC ≥95%) proportions on MDC Switched				p-value	Absolute Adherence (PDC ≥95%) proportions on MDC Unswitched				p-value
	Females	95%CI	Males	95%CI		Females	95%CI	Males	95%CI		Females	95%CI	Males	95%CI	
6 months	**68.3%**	62.24-73.7	**59.3%**	50.3-67.75	0.01078*	**70.7%**	57.99-80.82	**80.8%**	62.12-91.49	0.332	**63.3%**	55.69-70.21	**66.7%**	58.05-74.3	<0.0001*
	(n=177)		(n=70)			(n=41)		(n=21)			(n=105)		(n=84)		
12 months	**62.5%**	56.51-68.22	**51.3%**	42.33-60.15	0.0394*	**77.0%**	69.26-83.33	**66.3%**	55.58-75.52	0.0819	**62.5%**	23.3-43.57	**51.3%**	30.74-53.73	0.2187
	(n=162)		(n=60)			(n=104)		(n=55)			(n=28)		(n=28)		
24 months	**53.5%**	47.4-59.53	**45.2%**	36.42-54.32	0.13888	**73.5%**	65.8-79.94	**67.7%**	57.96-76.08	0.3271	**19.7%**	12.13-30.42	**28.6%**	17.85-42.41	0.25848
	(n=137)		(n=52)			(n=108)		(n=67)			(n=14)		(n=14)		

Legend: FDC=fixed dose combination, MDC=multiple dose combination regimen * statistically significant when compared to FDC

Discussion

The results were presented using Mean PDC at 6, 12 and 24 months for the 3 study groups, FDC, MDC Switched and MDC Unswitched, calculated over a period of 84 days at each study period. Absolute Adherence was defined as PD ≥ 95%, a standard acceptable for patients on ART to ensure viral suppression (Kim et al. 2014). In this study, a comparison of the level of adherence was done between the FDC regimen and the Unswitched MDC regimen, and between FDC and the MDC Switched regimen. A comparison of adherence was also done between females within each of the groups. Retention in care was reported indicated by number of clients who were retained on treatment, the number of those that were lost to follow up after 90 days and those that died whilst on ART treatment.

The study found that in spite of the implementation of a Fixed Dose Combination regimen mean PDC for FDC was below the acceptable standards of 80% for general medicines and, was below the Absolute adherence standard of 95% for antiretroviral treatment. The proportion of participants demonstrating Absolute adherence was only 65.5% for FDC at 6 months, which declined to 59% and 50.9% at 12 and 24 months respectively. Although these results show improvement from adherence levels indicated in earlier studies done in similar rural setting in SA before the introduction of FDC (Van Dyk , 2011)which found that only 40% of clients were able to achieve absolute adherence on ART, this is still lower than other African studies where adherence was found to be 77%, and comparable to rates in developed countries (Eyasu, 2015).

Of interest, a finding of this study indicated that the group that switched from multiple dose regimens to Fixed Dose regimen had an Absolute Adherence that surpassed that of the FDC group, with this being statistically significant at 12 and 24 months. The level of adherence for this group was almost constant over time, indicating low decline from 6 months to 24 months. This finding suggests that as these patients were no longer naïve when switched to a regimen with a much reduced pill load, from a more complex regimen, adherence improved for these patients compared to their previous peers on MDC and also surpassed those started on FDC. The effect of revived motivation by experienced patients starting a more simplified regimen could be an explanation for the improved adherence for these patients as explained by Schroeder et al. (2004), who conducted a Cochrane systematic review of adherence on patients on blood pressure medication which found that simplifying a drug regimen resulted in relative increase in adherence from 8 to 19 % (almost two-fold).

This study demonstrated that there was a significant difference in mean PDC and absolute adherence between fixed dose combination and multiple dose combination unswitched group, at 12 and 24 months. This was in agreement with another study done previously that showed advantage of using fixed dose combination over those regimens with more complex or frequently administered regimens (Deeks, et al, 2010). This above finding was also in agreement with the Colorado study in USA (Langness et al, 2015) and the meta-analysis study done in South Africa (Srivastava et al, 2013) which demonstrated the more complex the regimen, the less adherent the patient to the treatment.

However, this study found that at 6 months, absolute adherence was not significantly different between the FDC and MDC Unswitched group. Other factors related to non-adherence at start of treatment on FDC could have compromised the expected level of adherence early on in treatment, in support of Haochu's findings that side effects and drug toxicity could compromise adherence (Haochu, 2018). Patient- provider relationships, adherence support provided as well as other health systems issues related to access to health services are additional factors that compromise adherence to treatment (Naidoo, 2011).

Mean PDC and Absolute Adherence for FDC and MDC unswitched in this study declined over time, with the worst adherence demonstrated at 24 months. This finding is in agreement with a meta-analysis study done in South Africa that showed that persistence on treatment to oral therapies with both single dose and multiple dose regimens declined with time, with no significant differences noted between the two regimens over time (Srivastava et al, 2013). In this study however, absolute adherence on MDC unswitched group declined faster than FDC and MDC

Switched groups. Even though MDC Unswitched group had equal adherence rates with FDC and MDC switched at 6 months, persistence of adherence declined much more than FDC at 24 months. Medication persistence is said to be determined by primary adherence at start of treatment (Raebel M. et al., 2013). Persistence on treatment on the MDC Switched group remained high.

This study demonstrated a significant difference in mean PDC between males and females only for FDC group at 12 and 24 months, but not at 6 months. Absolute adherence was significantly higher for females in the FDC Group, but was found higher for males than females in the MDC unswitched group, though this was statistically not significant. This suggests that females are less able to adhere to more complex treatment regimens, however as time progressed to 24 months there was no significant difference in adherence between the two genders. The superiority of females over males in absolute adherence for FDC at 6 and 12 months is in agreement with Melaku's study conducted in Kwa-Thema SA in 2016 (Melaku et al. 2016). Although the Kwa-Thema study was not able to distinguish between the different treatment regimens used by the participants; in this study the findings of females being more adherent to ART than males could not be confirmed with MDC Switched and MDC Non switched groups. Absolute adherence in this study was relatively lower than the kwa-Thema study for both females (80.2%) and males (69.9%). This may be due to the methods used to assess adherence which was mainly self- reports by study participants in the Kwa Thema study, while this study used Proportion of days covered by patients

This study found that there was a progressive increase in the numbers of participants switched from MDC to FDC, from 102 after 6 months, to 255 at 12 months, and to 288 at 24 months. This suggests that there was compliance, though slow, with the ART treatment guidelines stating the use FDCs for patients on first line regimen (SA HIV/AIDS Treatment guidelines 2013).

Strengths and limitations of the study

The sample size of the study with 800 participants was relatively representative of the population of FDC and MDC treatment in the district under study with 26 461 patients on ART treatment at the time of data collection (SA District Health Information Systems, 2013). The sample size was estimated by using the formula as discussed by Glenn, 1992.

As part of the limitations, this study did not investigate other factors contributing to barriers to adherence to treatment other than pill count, and gender, including presence of side effects and adverse drug reactions on the different drug regimen, as safety and toxicity are also known to be significant factors contributing to non-adherence. This was due to incompleteness of clinical

information recorded by clinicians in the patients' health records. A triangulation of data collected using patient interviews would have assisted in determining other factors contributing to non-adherence other than complexity of regimen and the frequency of doses taken.

Conclusions

This study demonstrated that adherence to treatment on the fixed dose combination ART regimen was significantly better than that of treatment-naïve ART patients on multiple dose regimens. There was a high proportion of days covered and better retention to care with FDC compared to MDC regimen; however, absolute adherence was only significantly higher for the FDC regimen after 6 months of starting ART. This study also found that switching patients from a more complex regimen to a simpler regimen with less pill load and dosing frequency resulted in even better adherence for those patients, than those that were treatment naïve on FDC. The reluctance of clinicians to switch non-treatment naïve ART patients that were considered clinically stable on multiple dose regimens to FDC was not justified. The introduction of a fixed dose regimen as part of the South African ART Guidelines in December 2012 was a significant step towards improving patient adherence to ART treatment. This study also concluded that introduction of the FDC regimen did not bridge the adherence gap between females and males. A further investigation was needed to determine the effect fixed dose combination regimens have on ART treatment naïve patients on clinical outcomes compared to multiple dose regimens and the effect of switching non-treatment naïve patients from complex to simpler regimens.

REFERENCES

1. Armstrong B. et al. 2015. *Single tablet regimen usage and efficacy in treatment of HIV infection in Australia.* Aids Research and Treatment. 20 September 2016

2. Cahn P.et al. 2014. *Dual therapy with lipinovir and ritanovir plus lamivudine versus triple therapy with lipinavir and ritanovir plus two nucleotide reverse transcriptase inhibitorsin anti-retroviral therapy naïve adults with hiv-1 infection; 48 week results of the randomised , open label , non-inferiority GARDEL trial*. Lancet Infect Dis.2014nJul 14(7): 572-80, cited by Sax P in Journal watch AIDS Clinical care.

3. CDC, 2015. *Calculating Proportion of days covered for antihypertensivesa nd Antidiabetic Medications: An evaluation Guide for grantees.* Centres for Disease control and prevention. Aug 2015.

4. Davies, N. 2013. *Fixed-dose combination for adults accessing antiretroviral therapy* . SAJHIVMED. March 2013, Vol. 14, No. 1

5. Deeks E. et al., 2010.*Efavirenz/emtricitabine/tenofovir disoproxil fumarate single-tablet regimen (Atripla®): a review of its use in the management of HIV infection*.Drugs. 2010 Dec 3; 70(17):2315-38.

6. Melaku Z., Eyassu A. 2016. *Adherence to antiretroviral therapy among HIV and Aids patients at the Kwa-Thema clinic in Gauteng Province South Africa*. Afr.J primary Health care fam Med. 2016; 8(2): 924

7. Friedland G et al., 1999. *Attaining higher goals in HIV treatment: the central importance of adherence*. AIDS 1999

8. Glanz K, et al. 2002. *Health Behaviour and Health education. Theory, research and practice.* San Fransisco: Wiley & sons.

9. Glenn D. 1992. *Determining sample size*. University of Florida

10. Guidelines for the Use of Anti-retroviral agents in HIV-1 infected Adults and Adolescent. Available at http://aidsinfo.nih.gov/guideless/html/1/adult-and –adolescent-arv-guidelines/30/adherence, Assessed on 03 August 2016.

11. Haochu L.2018. *The Role of ARV associated adverse drug reactions in influencing adherence amongst HIV Infected Individuals*. Aids Behaviour. 1 Feb 2018

12. Hirasen K. et al. 2018. *The right combination- treatment outcomes among HIV positive patients initiating first line fixed dose antiretroviral therapy in a public sector HIV clinic in Johaneesburg, South Africa.* Clinical epidermiology, 2018; 10: 17-29

13. Homar F, 2012. *Cost analysis of HIV treatment and drug-related adverse events when fixed dose combinations of antiretrovirals were stopped, versus continuation with FDC'.s*. Health Econ Rev, 2012:2;16, Sep 2012.

14. Kader R, Seedat S. 2014. *Hazardous and Harmful use of alcohol and/ or other Drugs and Health status Among South African Patients attending HIV Clinics*. AIDS and Behaviour 18.3 : 524-34

15. Keith H.2014. *Incomplete Adherence Linked to greater Risk for Residual Low level Viremia.* AIDS 2014 Jan 14; 28:181

16. Kim S-H, Gerver SM, Fidler S, Ward H. *Adherence to antiretroviral therapy in adolescents living with HIV: systematic review and meta-analysis*. *AIDS (London, England)*. 2014;28(13):1945-1956.

17. Kipp W., et al., 2010. *Gender differences in antiretroviral treatment outcomes of HIV patients in rural Uganda.* AIDS Care, 2010 March; 22(3): 271-8

18. Khopotso B. 2012. Simplifying Aids *Treatment*. The centre for the study of Aids, Dec 2012, 20:05.

19. Kling J. 2014. *Once daily Combo outperforms Twice daily in COPD*. Available at http://www.medscape.com. American College of physicians, Oct 2014. Assessed on 09 November 2016.

20. Langness J et al.,, 2014. *Comparison of adherence rates for antiretroviral, blood pressure or mental health medications for HIV positive patients at an academic medical centre outpatient pharmacy*. J Manage Care Spec Pharm. 2014Aug; 20(8): 809-14

21. Marconi V. 2014. *Early Warning Indicators for Virological failure in the Southern African Context.* AWACC Conference 2014.

22. Marconi V. 2013. *How early should we start treatment?* Plos Med 103 Dec 10: 31001568

23. Marconi V et al .2008. *Prevalence of HIV-1 drug resistance after failure of a first highly active anti-retroviral therapy regimen in Kwazulu natal. South Africa*. Available at www.reserachgate.net/piblication. Assessed on 15 October 2016.

24. Naidoo P.2006. *Barriers to HIV Care and treatment by doctors: A review of the literature*. SA FamPract 2006; 48(2): 55

25. Olisah O, Baiyewu O, Sheikh T. 2010. *Adherence to highly active anti-retroviral therapyin depressed patients with HIV/AIDS attending a Nigerian University teaching hospital clinic.* Afr. J Psychiatry2010,13:275-279

26. Orom, H , Homish DL, Homish, GG. 2014. *Quality of physician-patient relationships is associated with the influence of physician treatment recommendations among patients with prostate cancer who chose active surveillance*. Urologic Oncology [2014, 32(4):396-402]

27. Parry C. 2014. *Hazardous and harmful use of alcohol and / or other drugs and Health status among South African patients Attending HIV clinics.* Aids and Behaviour 18.3 (Mar 2014: 525-34.

28. Pujari, S. 2008.*Effectiveness and safety of generic fixed-dose combination of tenofovir/ emtricitabine/ efavirenz in HIV-1-infected patients in Western India.* Medscape journal of medicine 10.8(2008): 196.

29. Raebel M. 2013. *Standardising terminology and definitions of medication adherence and persistence in research employing electronic databases.* Nchi. nlm.gov

30. San Lio MM, et al., 2008. *Evaluating adherence to highly active antiretroviral therapy with use of pill counts and viral load measurement in the drug resources enhancement against AIDS and malnutrition program in Mozambique*. Clinical Infectious Diseases, Volume 46, Issue 19. 15 May 2008, pages 1609-1616

31. Schneider H. 2006. *Health Systems and access to antiretroviral drugs for HIV in Southern Africa: service delivery and human resources challenges*. Reproductive health matters 14(27), 12-23.

32. Schroeder O. 2011. *Loyalty programms: Generalizations on their adoption*, effectiveness and design

33. Schroeder K. et al., 2004. *How can we improve adherence to blood-lowering medication? Systematic review of randomised controlled trials.* Archives of Internal medicine

34. Serebruany V. 2008. *Bleeding risks of combination vs single antiplatelet therapy: a meta-analysis of 18 randomised trials.* Fundamental and clinical pharmacology, Vol 22, issue 3. 15 May 2008.

35. Srivastava P, 2013. *Management of HIV AIDS. https/en.m.wikipedia.* Downloaded on 05 January 2018.

36. Steel G. et al., 2007. *Development of a Multi-Method Tool to measure ART Adherence in Resource –Constrained Settings: The South Africa Experience*. Rational Pharmaceutical Management Plus Program. Management Sciences for Health.

37. Stone VE et al. 2001. *Antiretroviral Regimen Complexity, Self-Reported Adherence, and HIV Patients' Understanding of their regimens: Survey of Women in the HER Study*. Journal of Acquired Immune Deficiency Syndromes: October1, 2001.

38. Stone VE, 2001.*Strategies for Optimizing Adherence to Highly Active Antiretroviral Therapy: Lessons from Research and Clinical Practice*. Oxford Journals, Medicine, Clinical Infectious Diseases, Volume 33, Issue 6, 865-872.

39. Suarez-Garcia I et al.2014. *Compliance with HIV Treatment Guidelines and Its effect on Outcomes*. HIV Med 2014 Feb 15:86

40. Thompson M, et al. 2012. *Guidelines for improving entry into and retention in careand anti-retroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel*. Ann Intern Med, 2012, Jun 5; 156 (11)

41. uThukela District Health Plan 2013/14. http:/www.kznhealth.gov.za. Accessed on 15 May 2016.

42. Van Dyk AC. 2011. Differences between patients who do and do not adhere to antiretroviral therapy. J Assoc Nurses AIDS Care. 2011 July- Aug.

43. Vermeer A. 2008. The psychosocial problems of children with HIV/AIDS in antiretroviral treatment. A longitudinal study.

44. Ware NC, Wyatt MA, Geng EH, et al.2013. *Toward an understanding of disengagement from HIV treatment and care in sub-Saharan Africa: A qualitative study*. PLoS Med2013;10:e1001369.; discussion e1001369.

After having ascertained that the proportion of patients achieving absolute adherence levels of 90% were only 65.5% at 6 months and decreasing to 50.9% at 24 months for a tenofovir/emtricitabine/ efavirenz based fixed dose combination regimen in chapter 2 a paper titled "*Impact of Fixed Dose Combination ART drug regimens on Viral Load suppression and Clinical Outcomes in a rural setting in South Africa: a retrospective longitudinal study"* was prepared. The impact of the tenofovir/ emtricitabine and efavirenz based fixed dose combination on viral load suppression, immunological response recovery by assessing mean C4 count over time, and on clinical outcomes including retention to care and deaths rates was evaluated compared to multiple dose regimens and those patients that switched from a multiple dose to a fixed dose regimen. A manuscript was prepared following the guidelines of BMC Public Health, and presented in Chapter 3 below.

CHAPTER 3

Impact of fixed dose combination ART drug regimen on viral load suppression and clinical outcomes in a rural setting in South Africa: a retrospective longitudinal study.

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Abstract

Background

The tenofovir /emtricitabine/efavirenz fixed dose combination (FDC) introduced to improve adherence in South Africa in 2013 is only able to achieve at most 65% absolute adherence rates. The study aimed to evaluate viral load suppression, immunological response of ART treatment), retention to care and death rates as determinants of clinical outcome of ART naïve patients on FDC compared to those on multiple dose regimens (MDC).

Methods

An institution based, adult patient retrospective pharmacy record review was conducted at four facilities rendering ART services of Uthukela District, Kwa-Zulu Natal, initiated from January 2013 to December 2013. 800 records, with 400 sampled from each of FDC and other MDC regimens were selected. A comparison was done between FDC and MDC regimens on Viral load (VL) suppression, mean Cd4 count change, retention in care and death rates were determined for each group at 6, 12 and 24 months after initiation of ART. Correlation between proportion of days covered (PDC) on treatment and VL suppression was evaluated.

Results

At 0-6 months 85 patients switched from MDC to FDC, at 12 months 220 had switched, and at 24 months 252, forming a third group(MDC-unswitched). Overall VL suppression at 6, 12 and 24 months for FDC was 97%(249/256 tests), 86.2%(145/167) and 89.3%(191/124) respectively. That of MDC-unswitched was 81.8%(23/27), 82%(89/102) and 56%(153/181), p value <0.05 at 6 and 24 months, and for MDC-switched was 85.5%(23/27); 87.3%(89/102) and 84.5%(153/181) p values >0.05 compared to FDC. VL suppression was higher for PDC≥95%. With PDC below 50% VL suppression for FDC was 93% (31/33), and MDC-unswitched 80% (8/10), p value<0.05 compared to FDC. VL suppression was positively correlated to PDC at 6 and 12 months with FDC, but not at 24 months. The mean Cd4 was higher for MDC than FDC at 12 months, but was sustained for FDC at 24 months. A strong negative correlation was found between the female gender and vital load suppression for FDC and MDC groups. No positive correlation could be found between gender and Mean Cd4 count The retention rate reduced over time for all groups, with FDC being 91.2% (363/400) at 24 months, 92.5% (233/252) for MDC switched p value> 0.05 compared to FDC, and 81.1% (120/ 148) for MDC unswitched, p value < 0.05 compared to FDC. At 24 months the death rate for FDC was 4.75% (19/400), that of MDC switched was 1.59% (2/252), and for MDC unswitched 17.57% (26/148), p value < 0.05 compared to FDC.

Conclusions

This study demonstrated that overall VL suppression for FDC was higher than MDC unswitched regimens at 6 and 24 months, and similar to MDC-switched at 12 and 24 months. FDC demonstrated high VL suppression even at low levels of adherence but this could not be maintained beyond 6 months. The results suggested that the Tenofivir based FDC demonstrated likelihood to higher resistance of viral mutations within the first 6 months of treatment. For PDC≥95% patients switched to FDC had VL suppression similar to FDC at 12 and 24 months. Immune recovery was sustained better on FDC than MDC. Deaths rates were three times lower for FDC than MDC-unswitched. The strong negative correlation was found with female adherence and viral load suppression even for FDC, suggests that other factors, other than pill load could be contributing to reduced viral load suppression rates for these patients inspite of demonstrating higher adherence rates than males. Further research is suggested to evaluate this further.

Keywords: Fixed Dose combination, multiple dose regimens, Viral Load suppression, Mean Cd4 count, Retention in care, Death rates, South Africa

Background

The Introduction of antiretroviral treatment in SA has resulted in major improved health outcomes; however nonadherence to ART treatment still remains a challenge. The strategy of introducing a fixed dose combination ART regimen (emtricitabine/ efavirenz/ tenofovir), to improve adherence and thus improve viral suppression and clinical outcomes (Davies, 2013) needs to be evaluated to determine if gains intended have been achieved.

The SA government in 2016 introduced a Vision 90-90-90 strategy with the aim of ensuring that 90% of the infected population knows their HIV status, that 90% of those that tested positive are started on treatment; and that 90% of those are virally suppressed. Year to year targets are set such that by 2020 this 90-90-90 vision is realised. 'Treatment as prevention' is also a core pillar of the national HIV/AIDS Strategy, which in turn requires patients to be virally suppressed throughout their life time.

A study conducted by Melaku et al. (2016) in South Africa found that adherence rates to ART were 74%, which were lower than the 95% levels of adherence needed to suppress the HIV virus. The study also indicated that females had a higher adherence of 80.2% compared to that of males which was 69.9%. The HER study in the USA showed that there is direct correlation between adherence and viral load suppression. Virologic failure rose with decreasing levels of adherence (Stone, 2001). HER study also demonstrated that Factors predicting lower adherence more frequent antiretroviral dosing, shorter duration of antiretroviral use, younger age, lower initial CD4 lymphocyte count and medication side effects. Tenofovir/ emtricitabine and efavirenz regimen have a potential to cause adverse drug reactions including compromised sleep quality, as efavirenz can cause insomnia and unusual dreams, and tenofovir can cause bone loss and kidney function impairment (Hingleyman, 2016). These side effects have a potential to reduce adherence to treatment. Irregular adherence to ART treatments may result in a definitive loss of efficacy of the therapeutic regimen and can lead to the development of resistance to the antiretroviral agents that are used (Homar et al. 2012).

Fixed dose combination antiretroviral therapy have demonstrated efficacy in suppressing HIV replication, improve immune function and decrease HIV related morbidity and mortality (Armstrong et al. 2015). FDC's lead to simplification of ART therapy compared with free drug regimens, which in turn improves quality of life and adherence to treatment (Masserli, 2007). Research conducted in India showed that a fixed dose combination of generic TDF/FTC/EFV was effective, and able to achieve viral suppression of 96% at 6 months for ARV –naïve and experienced patients (Pujari et al. 2008). A study by Deeks et al. in 2010 also demonstrated

advantage of using fixed dose combination over those regimens with more complex or frequently administered regimens.

A retrospective study conducted at Son Llàtzer Hospital where officials opted to discontinue FDC containing emtricitabine, such as AtriplaTM (efavirenz, emtricitabine, and tenofovir), similar to one used in SA, in favour of the administration of the separate component drugs , due to lower cost of generic lamivudine, indicated that discontinuation of FDC treatment and the replacement with the administration of separate antiretroviral agents could lead to an increase in healthcare costs due to the higher rate of adverse events that was observed with the discontinuation of FDCs. A study conducted in Barcelona found that patients who were virally suppressed and were switched to Atripla, were able to be suppressed for 6 months even when skipping doses for a day (Martinez et al. 2016). The study also found that taking once-daily *Atripla* resulted in suppressed viral load (below 37 copies/ml) for at least two years, with CD4 count above 350 cells/mm^3. No history of virological failure could be found, and no known resistance to efavirenz in this study.

Disadvantages of fixed drug combinations include reduced flexibility in dosing, exposure of patients to drugs that they do not need possible increased risk of adverse side effects, without increase in therapeutic benefit (Hennekens, 2008). Fixed dose combinations and once a day dosing regimens may also result in higher peaks of drug concentration reached that might result in toxic doses reached and increased side effects and adverse reactions of the drugs. These in turn if not monitored may reduce the intended improved adherence.

Multiple-dose regimens were often found to be related non- adherent to treatment, resulting in poor clinical outcomes indicated by clinical presentation of Opportunistic Infections whilst on treatment and poor virological suppression. (Ajose, 2012).Emtricitabine and lamivudine are nucleoside analogue reverse transcriptase inhibitors, similar in structure and antiretroviral activity. Studies however suggest that generic single lamivudine may be associated with higher rates of M1841/V mutations that could result in viral rebound and treatment failure. The Son Llàtzer Hospital study by (Homar et al.2012) however could not find any significant difference in virological suppression between those on FDC and those on single drugs. The CP-054 study found that patients previously on FDC Atripla (emtricitabine/ efavirenz/ tenofovir) had to be changed to FDC (emtricitabine/ rilpivirine/Tenofovir) due to side effects and drug interactions related to efavirenz (Chavez, 2015). This has significance as the first line ART regimen treatment in SA is Efavirenz based.

A study comparing adherence and Cd4 count found that adherence levels outperformed CD4 count changes when used to detect current virologic failure in the first year. CD4 count and

adherence could be used in identifying patients at very low risk of virologic failure (Bisson et al. 2008). A study was conducted at Uthukela district from January to December 2016 to compare adherence of a tenofovir/emtricitabine/ efavirenz based fixed dose combination regimen to multiple dose regimens. The results of the study suggested that the proportion of patients achieving absolute adherence levels of 90% were only 65.5% at 6 months and decreasing to 50.9% at 24 months for the fixed dose combination regimen. A further study was then necessary to establish effect of fixed dose ART regimen on clinical outcomes, including viral Load suppression, immunological response, and mortality, compared to the multiple dose regimens. A huge adherence gap previously identified between males and females also needed further investigation in terms of clinical outcome to inform practice in the management of patients.

Methods

Study Design

An institution based, comparison retrospective longitudinal study was conducted at 4 Health facilities of Uthukela District, Kwa-Zulu Natal.

Study area and Period

The study was conducted from January 2016 to December 2017 at four Health facilities that were rendering comprehensive ART services.

Source and study population

Patient record retrospective reviews of adult patients who were ART naïve on initiation of antiretroviral therapy were conducted. The study subjects were initiated on the 1st line treatment regimen according the South African ART Treatment guidelines (2013). The study subjects were randomly selected from 4 health facilities in the district, stratified to allow one facility from each level of care, to include: 1 Regional hospital,1 district hospital, 1 Community Health Centre, and 1 Primary health care facility (randomly selected from the 4 local municipalities that make up the district.

Study subjects were stratified according to the two groups:

Group 1: Patients initiated on Fixed Dose Combination (FDC) ART regimen; of Tenofovir, Emtricitabine and Efavirenz, taken once a day**.**

Group 2: Patients initiated on any other multiple- dose ART 1st line regimen.

Inclusion Criteria

Study subjects were Adult patients (above 18 years of age) who had been on 1st line ARV treatment. Only those patients who were ARV naïve on initiation of ART therapy were included in the study.

Exclusion Criteria

Patients younger than 18 years

Patients not on antiretroviral therapy

Patients presenting with any other known comorbid condition on initiation (for an example; TB, opportunistic infections, diabetes, and hypertension).

Patients on 2nd line regimens

Pregnant women that would have been exposed to the PMTCT programme before initiation on HAART.

Sampling Procedure

Sampling of Facilities

Data was collected from 4 health facilities in the district, one facility at each level of care, to include: 1 Regional hospital,1 district hospital, 1 Community Health Centre, and 1 Primary health care facility randomly selected from the 4 sub-districts using stratified random selection from the 4 local municipalities in the district.

Procedures for selection of Study Subjects

Study subjects were patients who started ART therapy in January 2013 to December 2013. The subjects were selected from each of the 4 study facilities, and were stratified according to the ARV treatment regimen they have been initiated on. Study subjects should have been on 1st line ART regimen and should have been on treatment for a minimum period of 3 months, and were stratified into two groups as follows:.

Group 1: Patients on Fixed Dose ARV combination of Tenofovir, Emtricitabine and Efavirenz, taken once a day**.**

Group 2: Patients on multiple- dose, 1st line ART regimens.

Study participants were sampled from a total sample frame of 4357 patients over the same period as the FDC group. One patient on the study later found to be younger than 18 years, and was excluded from the study, leaving a total sample size of 399 patients.

Sample Size

Using a formula by Naing et al, a minimum of 328 participants for each regimen group was required to detect at least 10% difference, a power of 80%, and 95% confidence interval. The sample size was estimated by using the formula: n = P (1-P) (Z-α/2/E), where P = total number of clients on treatment, (Z - α/2) = a constant code representing 95 % of confidence [1.96], E = margin of error [+/- 0.05] (Glenn, 1992). An assumption was made to detect at least 10 % (P = 10%) using the above formula. To accommodate for loss to follow up and drop outs 20% was added to the minimum sample size, a maximum of 400 participants per study group was used in this study. A total sample size of 400 patients on Fixed Dose regimen and 400 patients on multiple dose regimens were included in the final assumption of the sample size. A total Sample size of 800 participants formed the cohort for the study. This maximum sample size was divided among the four facilities included in the study. 100 patients were randomly selected from each of the 4 facilities for fixed dose combination and multiple dose regimens, respectively, using the formula (n+×) based on total number of patients per type of regimen in each facility. For example for facility identified as PHC, with 341 patients on multiple dose, the formula n+3 was used for selecting 100 clinical chart records

Data Collection tools and Procedures

Data was collected using a pretested structured data collection tool administered by 3 trained health care workers. The tool was designed to capture the patients file number, ART regimen, ART start date, age, gender, and clinical markers Viral load, Cd4 count , laboratory findings, presence of opportunistic infections, and clinical outcomes of whether a patient remained on treatment, died or was lost to follow up, at baseline, 6,12 and 24 months, as designed in appendix 8. Facility held ART Clinical chart records were used to collect clinical information. The data from patient ART clinical charts was triangulated with data from an electronic data information management system, known as *3–Tier*, and with other laboratory records available in the facility. Pharmacy refill records were used to identify adherence to diarized drug collections appointment dates.

To determine Drug Effectiveness Clinical Outcomes were calculated for each of the study groups

a) Viral Load suppression as a clinical marker for ART effectiveness was measured at 6 months, 12 months and at 24 months, for each of the study subjects. Viral load counts of less than 400 copies per millilitre of blood, were considered to be suppressed. The Viral Load suppression rate was measured for each of the groups at 6 months, 12 months and 24 months of therapy.

b) The Mean CD4 count from was determined, at baseline, 6 months, 12 months and 24 month for the two groups.

c) The Proportion of patients Retained in Care was determined, at baseline, 6 months, 12 months and 24 month

d) The Death rate was determined at 6 months, 12 months and 24 months for each group

Data Quality assurance

Data was collected by using a pre-tested tool by trained health care providers. There was continuous supervision to control the data collection procedure. All the data, from each study site, was checked by the principal investigator, for completeness, clarity and consistency. The different sources of data were used for triangulation. Data was intensively cleaned before analysis.

Data processing and analysis

Data was coded and entered into different statistical tools, including Enterprise Miner and SPSS windows version 20 for further analysis. Adherence to HAART was assessed by using Proportion of days covered (PDC) calculated from using Pharmacy refill records and 3-Tier records. Absolute Adherence was measured by working out the number of days covered above 95%. Viral Load suppression was analysed by the Health workers and viral load was considered lower than suppressed if the viral count was lower than 400 copies per millilitres of blood and/or undetectable.

Bivariate logistic regression was used to check variables associated with the dependent variable. Odd ratios with 95% CI were computed and those variables found to have p-values of < 0.05 were considered significantly associated with the dependent variable. P values were used to find evidence of a significant difference between population means.

Only those files with available clinical parameters were considered to calculate viral load suppression and Mean Cd4 and not the total cohort at baseline. Those patients that had died were

also excluded from calculating the viral load suppression rate, however the retention rates and death rates were calculated based on the total cohort per regimen.

Ethical Considerations

Ethical clearance was obtained from the ethical review Committee of the University of Kwa-Zulu Natal. Permission was granted by the Provincial Department of Health. Approval was granted by the Uthukela District Director and the CEO's of the Health facilities, and letters of support were provided. Each caregiver and operational manager of the facilities or ART unit was adequately informed about the purpose of the study. Patient information was kept confidentially using patient codes instead of patient names, and the records were kept in password protected computers.

Results

Socio-demographic characteristics of the study subjects

Two groups of patients, on FDC and MDC, were included in this study. At baseline there were 400 participants from each group. The majority of the participants in both groups were females; with 67.5% (270/400) in the FDC group and 59.3% (237/400) in the MDC group .The median age of the FDC group was 33.1 ± 10.3 years while the median age for the MDC group was 32.9 ± 10.1 years.

A total of 400 prescriptions from the Multiple Dose combination group was comprised of 7 % Abacavir based multiple dose regimens, 5.25% Stavudine, 3.25% Zidovudine and 84.5 % Tenofovir based. The second NRTI for all these regimens was Lamivudine, and a third component of the HAART regimen was one of the NNRTI's either Efavirenz or Nevirapine, or Protease Inhibitor Lopinavir/ ritonavir.

Between 0 and 24 months of treatment from the MDC group, a total of 252 participants were switched to Fixed Dose Combination regimen and identified as MDC Switched. Multiple Dose group was assessed as two distinct sub-groups, those that switched to FDC and those that did not switch and remained on MDC. The assessment of adherence was conducted comparing the 3 groups: FDC, MDC Switched and MDC Unswitched.

Clinical Marker at baseline of the study subjects

At baseline, the mean Cd4 count was 181±123.87 cells/ mm3 for FDC (n=356) and 186±127.53 Cd4 cells/mm3 for MDC (n=337), there was no significant difference between the 2 groups Mean Cd4 (p value = 0.623).

ARV regimens used by study participants

At baseline 400 participants on the FDC were started on the 1 TFE Fixed dose combination regimens. This only changed at 24 months when 1 participants was changed to a second line regimen 2SEL, and one changed to T3N, leaving balance of 398 remaining on FDC (TFE).

Table 3.1 presents ART regimen breakdown and profile of participants that were switched, from baseline to 24 months, and that of those that remained on the MDC group as unswitched. At baseline 80.75% (323/400) of participants on MDC group were on 1 T3E, considered a generic equivalent to TFE with Emtricitabine in FDC and Lamivudine in the MDC Group. Between 0 to 6 months 85 participants were switched to the FDC (TFE), again between 7 to 12 months an additional 115 participants were switched to FDC to make a total of 220, and between 13 to 24 months 32 additional participants were changed from MDC to FDC to make a total of 252. Most of the participants that were switched had been on T3E MDC regimen at baseline.

Table 3.1: ART regimen breakdown of MDC, MDC Switched and MDC Unswitched group at baseline before switch to FDC

Baseline	**0-6 months**		**7-12 months**		**13-24 months**	
Baseline Regimen for MDC at baseline (N= 400)	Baseline Regimen for MDC Switched group to FDC at 0-6 months (N=85)	Baseline Regimen for MDC Unswitched group at 6 months (N=315)	Baseline Regimen for MDC Switched group to FDC at 7-12 months (N=220)	Baseline Regimen for MDC Unswitched group at 12 months (N=180)	Baseline Regimen for MDC Switched group to FDC at 13-24 months (N=252)	Baseline Regimen for MDC Unswitched group at 24 months (N=148)
1A3E= 6.75% (n=27)	1 S3E= 2.35%(n=2)	1 A3E= 8.57% (n=27)	1 A3E= 3.18% (n=7)	1A3E= 11.11% (n=20)	1A3E= 3.17%(n=8)	1A3E= 12.84% (n=19)
1A3N= 0.25% (n=1)	1 T3E= 85.88% (n=73)	1A3N=0.32% (n=1)	1S3E=3.18% (n=7)	1 A3N= 0.56% (n=1)	1S3E= 3.17% (n=8)	1A3N= 0.67% (n=1)
1S3E= 4.75% (n=19)	1 T3N= 3.53% (n=3)	1S3E=5.4% (n=17)	1T3E= 88.6% (n=195)	1S3E= 6.67% (n=12)	1T3E= 89.3% (n=225)	1S3E= 7.43% (n=11)
1S3L= 0.25% (n=1)	1 Z3E= 8.24% (n=7)	1S3L= 0.32% (n=1)	1TFN= 1.82% (n=4)	1 S3L = 0.56% (n=1)	1T3N= 1.59% (n=4)	1S3L= 0.67% (n=1)
1S3N= 0.25% (n=1)		1S3N= 0.32% (n=1)	1Z3E=3.18% (n=7)	1 S3N= 0.56% (n=1)	1Z3E= 2.78% (n=7)	1S3N- 0.67% (n=1)
1T3E= 80.75% (n=323)		1T3E=79.4% (n=250)		1T3E= 71.1% (n=128)		1T3E= 66.22% (n=98)
1T3L= 0.25% (n=1)		1T3L= 0.32% (n=1)		1T3L= 0.56% (n=1)		1T3L= 0.67% (n=1)
1T3N= 3.5% (n=14)		1T3N= 3.5% (n=11)		1T3N =5.56% (n=10)		1T3N= 6.78% (n=10)
1Z3E= 3.25% (n=13)		1Z3E= 1.9% (n=6)		1Z3E = 3.33% (n=6)		1Z3E = 4.05% (n=6)

Legend: 3= Lamivudine, A= Abacavir, E= Efavirenz, F= Emtricitabine, L= Lopinavir, Ritonavir comb, N= Nevirapine, S= Stavudine, T= Tenofovir, Z= Zidovudine, FDC= Fixed Dose Combination of Tenofovir/Emtricitabine and Efavirenz. MDC= Multiple Dose Combination

Comparison of Viral Load Suppression between FDC, MDC switched and MDC unswitched

Table 3.2 presents differences in the Proportion of study participants who had Viral Load Suppression at month 6, 12, and 24 between FDC, MDC witched and MDC unswitched.

VL suppression at 6 months for FDC was 97% (249/256), that of MDC switched 85% (23/27) at 6 months, p value < 0.05. At 12 months VL suppression for FDC was 86.8% (145/167) higher than that of MDC Unswitched that was 81.8% (72/88), p value < 0.05. MDC switched at 12 months was 87% (89/102) not statistically different to FDC, p value> 0.05.There was a progressive decline in VL suppression for MDC unswitched to 56.7% (17/30), but for FDC and MDC switched groups VL suppression remained high at 89.3% (191/214) and 84.5% (153/181) respectively, p value > 0,05.

Table 3.2 suggests that over time, for FDC, viral load suppression was maintained at levels above 80% at 6, 12 and 24 months, surpassing both MDC switched and MDC unswitched. MDC switched VL suppression almost remained a constant with a slight decline at 24 months. At 12 months there was no significant difference between VL suppression for FDC and MDC switched. At 24 months VL suppression declined drastically for MDC switched.

Table 3.2: Viral Load Suppression for FDC, MDC switched and MDC unswitched over time

DUR	FDC				MDC Switched					MDC UNSwitched				
	No. VL taken	VL Suppr	NR	95%CI	No. VL taken	VL Suppr	NR	95%CI	p value	No. VL taken	VL Suppr	NR	95%CI	p value
6	256	97.26% (n=249)	121	94.47-98.67	27	85.2% (n=23)	57	46.1-75.93	<0.0001	88	81.8% (n=72)	204	72.49-88.49	<0.0001
12	167	86.8% (n=145)	208	80.86-91.14	102	87.3% (n=89)	116	79.4-92.39	0.92034	37	82.2% (n=37)	109	68.67-90.7	0.42952
24	214	89.3% (n=191)	157	84.39-92.73	181	84.5% (n=153)	65	78.55-89.07	0.16452	30	56.7% (n=17)	90	39.2-72.63	<0.0001

Legend: No= number of tests done, VL suppr = Viral Load Suppression, NR= not recorded.

Adherence and Viral Load Suppression

Figure 3.1 represents the relationship of PDC with viral load suppression for FDC, MDC switched and MDC unswitched at 6, 12 and 24 months. MDC had a relatively higher PDC than FDC and MDC switched, but FDC had a higher proportion of participants that were virally suppressed. The FDC group achieved a 97% viral suppression at 6 months in spite of adherence rates of 65,5%, but thereafter at 12 months VL suppression was to 86.8% with adherence rates of 59% , to recover again at 24 months to 89% with adherence rates of 50.9%. At 6 months, viral suppression was almost similar with all the groups, in spite of MDC switched having a larger proportion of days covered on treatment.

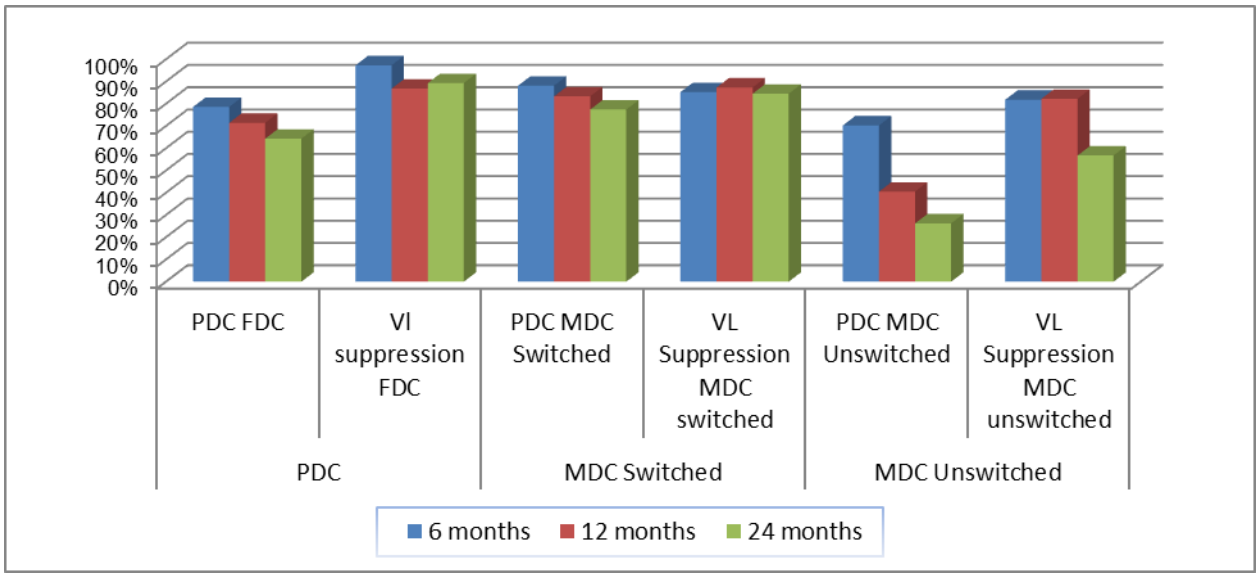

Figure 3.1: PDC and Viral load suppression over time, with FDC, MDC and MDC unswitched.

Viral load suppression at levels of adherence above ≥ 95%

Table 3.3 presents a comparison of Viral load for the participants on the three regimens at varying levels of adherence to treatment. At 6 months for patients who had PDC ≥ 95%, VL suppression for FDC was 98.3% (171 out of 174 tests) , for MDC switched it was 86.9% (20 out of 23 tests) and for MDC unswitched it was 81.4% (57 out of 70 tests). The difference in VL suppression between FDC and MDC switched, and between FDC and MDC unswitched was significant, with FDC demonstrating higher VL suppression, p value < 0.05. At 12 months there was no significant difference in VL suppression rates between FDC and the two other groups, p value > 0.05. At 24 months, there was no significant difference between VL suppression for FDC and MDC Switched. The difference in VL suppression was significant between FDC where VL suppressions was 92.4% (133 VL suppressed out of 144) and was 63.2% (12 VL suppressed out of 19) for MDC, p value < 0.05.At PDC≥95% at 6, 12 and 24 months Viral load suppression ranged between 89%-98% for FDC, remained constant at 87% for MDC switched, and VL suppression dropped from 81% at 6months, to 77% at 12 months and further to 6% at 24 months.

Viral load suppression at levels of adherence below (PDC < 50%)

For those participants that had PDC below 50% at 6 months, VL suppression for FDC was 93% (31/33), MDC-switched 50%(23/27) and MDC-unswitched 81.8%(72/88). The difference in VL suppression was significant between FDC and MDC switched (p value < 0.05) but not between

FDC and MDC unswitched (p value > 0.05). At 12 months VL suppression for FDC was lower than that of MDC switched (56.5% versus 76.9%) which in turn was also lower than that of MDC unswitched (95.5%), however the difference was only significant between FDC and MDC unswitched groups. At 24 months there was no statistically significant difference between VL suppression between FDC (76.6%) and MDC switched (88.9%) and between FDC and MDC unswitched (71.4%).

Table 3.3: Comparison between level of adherence and Viral Load suppression

6 months														
PDC	**FDC**				**MDC Switched**					**MDC Unswitched**				
	No.VL taken	**% VL Suppr**	**Not Rec**	**95%CI**	**No.VL taken**	**% VL Suppr**	**Not Rec**	**95% CI**	**p value**	**No.VL taken**	**% VL Suppr**	**Not Rec**	**95% CI**	**p value**
≥95%	**174** (n=247)	**98.3%** n=171	**73**	95.06-99.41	**23** (n=62)	**86.9%** n=20	**39**	67.88-95.46	**0.003**	**70** (n=189)	**81.4%** n=57	**119**	70.78-88.81	**<0.0001**
80-94%	**14** (n=21)	**85.7%** n=12	**7**	60.05-95.99	0 (n=2)	n=0	2			3 (n=6)	100.0% n=3	3	43.85-100	0.4839
65-79%	**32** (n=35)	**100%** n=32	**3**	89.28-100	**1** (n=13)	**100%** n=1	**12**	20.65-100	**<0.0001**	**5** (n=11)	**80%** n=4	**6**	37.55-96.38	0.1046
50-64%	**3** (n=6)	**100%** n=3	**3**	43.85-100	**1** (n=1)	100% n-1	0	20.65-100	**<0.001**	0 (n=1)		1		
<50%	**33** (n=68)	**93.3%** n=31	**35**	80.39-98.32	**2** (n=16)	**50%** n=1	**4**	1.49-35.38	**<0.0001**	**10** (n=85)	**80%** n=8	**75**	49.02-94.33	0.1835
N	**256**	**97.26% (n=249)**	**121**	**94.47-98.67**	**27**	**85.2% (n=23)**	**57**	**46.1-75.93**	**0.002**	**88**	**81.8% (n=72)**	**204**	**72.49-88.49**	**<0.0001**
T/O	1.5% (n=6)				1.18% (n=1)				0.8181	0.95% (n=3)				0.8572
Died	4.25% % (n=17)				0% (n=0)				0.0536	6.35% (n=20)				**0.0173**
Total	**400**				**85**					**315**				
12 months														
PDC	**FDC**				**MDC Switched**					**MDC Unswitched**				
	No.VL taken	**% VL Suppr**	**Not Rec**	**95%CI**	**No.VL taken**	**% VL Suppr**	**Not Rec**	**95% CI**	**p value**	**No.VL taken**	**% VL Suppr**	**Not Rec**	**95% CI**	**p value**
≥95%	**121** (n=222)	**89.3%** n=108	**101**	82.49-93.62	**77** (n=159)	**87.0%** n=67	**82**	77.71-92.79	0.6312	**18** (n=56)	**77.7%** n=14	**38**	54.79-91	0.1645
80-94%	**15** (n=22)	**100%** n=15	**7**	79.61-100	**2** (n=7)	**100%** n=2	**5**	34.24-100	**<0.0001**	**1** (n=1)	**0%** n=0	0	0-79.35	**<0.0001**
65-79%	**13** (n=33)	**84.6%** n=11	**20**	57.77-95.78	**9** (n=15)	**100%** n=9	**6**	70.09-100	0.2187	**4** (n=6)	**50%** n=2	**2**	15-85.0	0.1527
50-64%	3 (n=5)	**66.6%** n=2	2	20.77-93.85	**1** (n=2)	**100%** n=1	**1**	20.65-100	0.5029	**0** (n=1)		**1**		
<50%	**16** (n=94)	**56.3%** n=9	**78**	33.18-76.9	**13** (n=35)	**76.9%** n=10	**22**	49.74-91.82	0.246	**22** (n=90)	**95.5%** n=21	**68**	78.2-99.19	**0.0034**
N	**167**	**86.3% (n=145)**	**208**	**80.86-91.14**	**102**	**87.3% (n=89)**	**116**	**79.4-92.39**	**0.9203**	**37**	**82.2% (n=37)**	**109**	**68.67-90.7**	**0.4295**
T/O	1.5%(n=6)			0.69-3.23	0.91% (n=2)			0.25-3.25	0.5353	1.11% (n=2)				0.7114
Died	4.5% (n=18)			2.87-7.00	0% (n=0)			0.0-1.72	**0.0014**	13.33% (n=24)				**0.0001**
Total	**400**				**220**					**180**				
24 months														
PDC	**FDC**				**MDC Switched**					**MDC Unswitched**				
	No.VL taken	**% VL Suppr**	**Not Rec**	**95%CI**	**No.VL taken**	**% VL Suppr**	**Not Rec**	**95% CI**	**p value**	**No.VL taken**	**% VL Suppr**	**Not Rec**	**95% CI**	**p value**
≥95%	**144** (n=189)	**92.4%** n=133	**45**	86.84-95.68	**147** (n=175)	**86.4%** n=127	**28**	79.91-91.01	0.0989	**19** (n=28)	**63.2%** n=12	**9**	41.04-80.85	**0.0001**
80-94%	**11** (n=20)	**81.8%** n=9	**9**	52.3-94.86	**6** (n=6)	**50%** n=3	**0**	18.76-81.24	0.1676	**2** (n=2)	**0%** n=0	0	0-65.76	**0.0209**
65-79%	**28** (n=35)	**89.3%** n=25	**7**	72.81-96.29	**9** (n=10)	**66.7%** n=6	**1**	35.42-87.94	0.1096	**1** (n=1)	**0%** **n=0**	0	0-79.35	**0.0111**
50-64%	**1** (n=4)	**100.0%** n=1	**3**	20.65-100	1 (n=2)	**100.0%** n=1	**1**	20.65-100	<0.0001	**1** (n=1)	0%	0	0-79.35	0.1585
<50%	**30** (n=123)	**76.7%** n=23	**93**	59.08-88.21	**18** (n=53)	**88.9%** n=16	**35**	67.2-96.90	0.2937	**7** (n=88)	**71.4%** n=5	**81**	35.89-91.78	0.7718
N	**214**	**89.3% (n=191)**	**157**	**84.39-92.73**	**181**	**84.5% (n=153)**	**65**	**78.55-89.07**	**0.1645**	**30**	**56.7% (n=17)**	**90**	**39.2-72.63**	**<0.0001**
T/O	2.0% (n=8)			1.02-3.92	1.59% (n=4)			0.62-4.01	0.6965	1.35% (n=2)			0.37-4.79	0.5892
Died	4.75% (n=19)			3.07-7.33	1% (n=2)			0.22-2.84	**0.0051**	17.57% (n=26)			12.28-24.50	**<0.0001**
Total	**400**				**252**					**148**				

Legend: PDC= Proportion of days covered, FDC= Fixed Dose Combination regimen, MDC = Multiple dose combination regimen, % VL suppr= Percentage Viral Load Suppressed, Not Rec= Not recorded

Differences in PDC and Viral load Suppression between females and males in the FDC group

The results from table 3.4 present a comparison of PDC and viral load suppression between females and males for FDC. The results suggest that Females had higher Viral load suppression than males for FDC, at 6 months (97% vs 89.16%), this difference was only statistically significant, p values< 0.05. At 12 and 24 months males demonstrated a higher viral load suppression rate than females (83.05% versus 80%, and 83.05% vs 80% respectively), however this difference was not statistically significant, p value > 0.05.

Table 3.4: Differences in PDC and viral load suppression between females and males on FDC

Duration on Treatment	Means of PDC with FDC (out of 84 days)			Proportion of Viral load suppression on FDC						
	Females	Males	p-value	No of VL tests Females	Females Suppressed	%, with 95%CI	No of VL tests Males	Males Suppressed	%, with 95%CI	p-value
6 months	68±29.25 (n=259)	62±32.24 (n=118)	0.9353	178	97% (n=173)	93.59-98.79	83	89.16% (n=74)	80.66-94.99	**0.007***
12 months	64±32.40 (n=259)	53±37.25 (n=117)	**0.0068***	132	78.78% (n=104)	71.05-84.90	39	87.18 % (n=34)	73.29-94.40	0.242
24 months	57 ± 35.14 (n=256)	46 ± 39.87 (n=115)	**0.0067***	165	80% (n=132)	73.25-85.39	59	83.05% (n=49)	71.54-90.52	0.61

Legend: FDC= Fixed Dose combination regimen

Comparison in Cd4 count between FDC, MDC switched and MDC unswitched over time

Table 3.5 presents the mean differences in Mean CD4 count (cells per mm3 of blood) of study participants at month 6, 12, and 24 between FDC and MDC

At Baseline 356 out of 400 participants had CD4 tests done for FDC and the mean CD4 count was 181.54 cells/ mm3. For MDC 337 out of 400 participants had CD4 tests done and the mean CD4 count was 186.24 cells/ mm3 of blood. The results suggest that there was no Immunological difference in the two groups at baseline, p value < 0.05. At 6 months the difference in mean CD4 count was significant between FDC and MDC switched with MDC switched demonstrating lower mean Cd4 count. At 12 months there was a significant difference between FDC and MDC unswitched, with MDC switched having higher Mean Cd4 count.

At 6 months the mean Cd4 count for FDC was 319.8 cells/mm3 (28% increase) , at 12 months it was 404.83 cells/mm3 (28% increase) and at 24 months it was 457.29 cells/mm3 (26.6%). At 12 months there was a 123% recovery in Cd4 count from baseline. At 24 months, there was an overall 152.9% recovery from baseline. For MDC unswitched at 6 months there was an increase

of 51% from baseline, 168% at 12 months from baseline (78% increase from 6 months) and at 24 months Cd4 count dropped by 16%. For MDC switched Cd4 count recovered at 12 months by 100% from 6 months, however at 24 months this dropped by 13%

Table 3.5: Change in Cd4 cell count over time

	Mean CD4 count for FDC (cells/mm3)	**Mean Cd4 count for MDC Switched (cells/mm3)**	**p value**	**Mean CD4 count for MDC Unswitched (cells/mm3)**	***p value**	****P value**
Baseline	181.54±123.87	**N/A**		186.24±127.53	*0.623	
6 months	319.80±219.47	230 ± 153.33	*0.003144	280 ± 210.47	*0.135179	**0.71995
12 months	404.83±226.46	460.40±353.808	*0.178153	498.56±252.955	*0.000261	**0.414235
24 months	457.24±246.27	402.909±219.38	*0.182169	420.82±239.92	*0.175433	**0.657225

Legend: PDC=proportion of days covered, FDC=fixed dose combination, MDC=multiple dose combination. * statistical significance when compared to FDC. ** Statistical significance when comparing MDC switched to MDC Unswitched

Correlation between Gender, Absolute Adherence, Viral Load and Cd4 count at 6, 12 and 24 months

Table 3.6 presents correlation between Gender, Absolute adherence and viral load using Pearsons p value. The results suggest that there was negative correlation between adherence and gender at 6, 12 and 24 month, however, the results were not statistically significant. The results suggest that there was a strong negative significant correlation between gender and Viral Load suppression at 12 months and 24 months, but the negative correlation at 6 months was insignificant. There is strong significant positive correlation between Adherence and VL Load Suppression at 6 months and 12 months however though correlation is positive at 24 months this was not statistically significant.

Table 3.6: Correlation between Gender, Absolute adherence and viral load count over time

		Adherence						Viral load Suppression					
		FDC 6mths	FDC 12mths	FDC 24mths	MDC 6mths	MDC 12mths	MDC 24mths	FDC Suppr 6mths	FDC Suppr 12mths	FDC Suppr 24mths	MDC Suppr 6mths	MDC Suppr 12mths	MDC Suppr 24mths
Gender	Gender FDC	-0.076	-0.025	-0.061	0.011	0.033	0.02	-0.03	-.170**	-.129**	-0.042	0.052	0.009
	Gender MDC	-0.004	-0.004	-0.016	0.034	0.052	0.086	-0.008	-0.037	0.001	-0.007	0.034	-0.028
Adherence	FDC 6mths		.852**	.778**	-0.042	0.016	0.044	.262**	.293**	0.087	.103*	0.067	0.066
	FDC 12mths			.791**	-0.026	0.007	0.047	.261**	.225**	0.059	.123*	0.088	0.052
	FDC 24mths				-0.055	-0.011	0	.233**	.226**	0.061	0.09	0.072	0.057
Viral load Suppression	MDC 6mths					.802**	.740**	.226**	.122*	0.083	0.084	0.029	-0.063
	MDC 12mths						.856**	.189**	0.047	0.046	.157**	0.098	-0.042
	MDC 24mths							.200**	0.097	0.045	.105*	0.07	-0.066

Legend: *. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

PDC=proportion of days covered, FDC=fixed dose combination, MDC=multiple dose combination.

Retention to care

Table 7 presents retention in care and overall clinical outcomes over time for FDC, MDC switched and MDC unswitched. At 6 months out of the 400 participants in the FDC group, 368 (92%) were retained in care, 9 (2.25%) were lost to follow, 6 transferred out and 17 (4.25%) participants died. From MDC switched, of the 85 participants that were switched to FDC at the end of 6 months, 84 (98%) were retained on treatment and 1 was transferred out. From the 315 that remained on MDC unswitched 279 were retained on treatment, 13 (4.12%) were lost to follow up, 3 transferred out and 20 (6.3%) participants died. At 12 months duration on treatment, retention in care rate reduced to 91.8% for FDC, 04.5% for MDC switched and 83, .9% for MDC unswitched. At the end of the 24 month period, 2 patients from FDC were switched to a second line multiple dose regimen, leaving a total sample of 398. Of the 400 on FDC 363 (90.75. %) were retained, 8 (2%) were lost to follow up, 8 (2%) were transferred out and 19 (4.8%) died. From the original 400 participants on MDC, a total of 252 were switched at the end of 24 months to FDC, of those 233 (92.5%) were retained, 13 (3.15%) were lost to follow up, 4(1.58%) were transferred out, and 3 died (0.79%). Of the 148 that remained on MDC, 120 (81.1%) were retained, 2 (transferred out), and 26 (17.6%) participants died.

Death rates of FDC, MDC switched and MDC unswitched at 6, 12 and 24 months

Table 3.7 also presents death rates at month 6, 12, and 24 between FDC, MDC witched and MDC unswitched.

The death rate at 6 months for FDC was 4.25% (17/400), that of MDC switched 0% (0/85), and MDC unswitched 6.35% (20/315), with p value < 0.05 between FDC and MDC unswitched. Difference in death rates for MDC switched at 6 months was not statistically different to FDC, p value > 0.05. At 12 months the Death rate for FDC was 4.5% (18/400), for MDC Unswitched it was retained at 0% (0/220), and for MDC unswitched was 13.33% (24/180). At 24 months the death rate for FDC was 4.75% (19/400), that of MDC switched being the lowest at 1.59% (2/252), p value< 0.05, and for MDC unswitched 17.57% (6/148), p value < 0.05 compared to FDC.

There was a progressive increase in death rates for FDC and MDC unswitched from 6, 12 to 24 months, and from 12 to 24 months for MDC switched. The results suggest that there were significantly higher deaths rates for MDC unswitched than FDC, p value < 0.05, at 6, 12 and 24 months.

Table 3.7: Retention to care and death rates over time

6 MONTHS								
	FDC (n,%)	**95%CI**	**MDC Switched (n,%)**	**95%CI**	**P value**	**MDC Unswitched (n,%)**	**95%CI**	**P value**
Retained	**368** 92%	88.92-94.28	**84** 98.8%	93.63-99.79	0.0232	**279** 88.6%	84.58-91.63	0.00374
LTF	**9** 2.25%	1.19-4.22	**0** 0%	0-4.32	0.16152	**13** 4.12%	2.43-6.94	0.05744
T/O	**6** 1.50%	0.69-3.23	**1** 1.18%	0.21-6.37	0.8181	**3** 0.95%	0.32-2.76	0.85716
Died	**17** 4.25%	2.67-6.7	**0** 0%	0-4.32	0.0536	**20** 6.30%	4.15-9.6	0.01732
Total	**N=400**		**N=85**			**N=315**		
12 MONTHS								
	FDC (n,%)	**95% CI**	**MDC Switched (n,%)**	**95% CI**	**P value**	**MDC Unswitched (n,%)**	**95%CI**	**P value**
Retained	**367** 91.8%	88.92-94.28	**208** 94.5%	90.71-96.86	0.20054	**151** 83.9%	77.82-88.54	0.00466
LTF	**9** 2.25%	1.19-4.22	**10** 4.54%	2.49-8.17	0.11184	**3** 1.67%	0.57-4.79	0.64552
T/O	**6** 1.50%	0.69-3.23	**2** 0.90%	0.25-3.25	0.53526	**2** 12.20%	0.3-3.96	0.71138
Died	**18** 4.50%	2.67-6.7	**0** 0%	0-1.72	0.00142	**24** 13.33%	9.12-19.07	0.00014
Total	**N=400**		**N=220**			**N=180**		
24 MONTHS								
	FDC (n,%)	**95% CI**	**MDC Switched (n,%)**	**95% CI**	**P value**	**MDC Unswitched (n,%)**	**95% CI**	**P value**
Retained	**363** 91.2%	88.02-93.61	**233** 92.5%	88.52-95.12	0.57548	**120** 81.1%	74.01-86.57	0.001
LTF	**8** 2%	1.02-3.92	**13** 5.16%	3.04-8.36	0.0271	**0** o%	0-2.53	0.08186
T/O	**8** 2%	1.02-3.92	**4** 1.58%	0.62-4.01	0.69654	**2** 1.35%	0.37-4.79	0.61006
Died	**19** 4.75%	2.88-7.03	**2** 0.79%	0.22-2.84	0.00512	**26** 17.60%	12.28-24.5	<0.0001
Total	**400**		**252**			**148**		

Legend: PDC=proportion of days covered, FDC= fixed dose combination, MDC=multiple dose combination. T/O= Transfer out, LTF= Lost to follow up

Discussion

The study sought to find the effect of reduced pill load and regimen complexity on immunological response and clinical outcomes including retention to care. Participants on a Tenofovir based fixed dose combination were monitored for viral load suppression and Cd4 count recovery against those that were started on multiple dose regimens, and against those that were initially on a multiple dose regimen but later switched to the same fixed dose regimen, forming a third group from which the effect of switch to a fixed dose combination was reported on. Levels of adherence to the three regimens, FDC, MDC switched and MDC unswitched were compared over time, at 6 months, 12 months and 24 months on treatment, and the effect that had on immunological response. The difference in response between FDC and the two other groups was evaluated to determine the effect of fixed dose combination regimen. Viral load suppression was regarded as participant's viral load below 400 copies per mm^3 of blood.

The findings of this study suggest that even though the proportion of days covered for FDC was below the optimum level of absolute adherence of 95%, ranging from 78% at 6 months, 71% at 12 months and declining further to 64% at 24 months, the viral load suppression rate remained high, being 97% at 6 months, 87% at 12 months and 89% at 24 months. With PDC below 50%, VL suppression rates for FDC at 6 months were 93% at 6 months, but declined to 53% at 12 months, and recovered to 74% at 24 months. These findings seem to be in support of Martinez' et al. findings that even when skipping doses to three times a week on *Atripla,* viral load suppression can be maintained for 24 weeks (Martinez et al. 2016). This indicates the potency of the regimen in spite of reduced adherence. In this study, however, VL suppression rates were only 53% at 12 months, and one patient was switched to second line regimen due to treatment failure contrary to Martinez et al study which found no virological failure at 24 months for patients on the daily dose of *Atripla*.

In this study there was a strong positive correlation found between proportion of days covered on treatment and VL suppression at 6 and 12 months, but there was no significant correlation at 24 months. This was partly in agreement with Stone (2001) who stated that as adherence increased, viral load suppression also increased. The limited correlation with high VL suppression in spite of lower adherence at 24 months, could be a confirmation of emergence of viral mutations over time, but VL suppression for FDC was still better than multiple dose regimens; this is in agreement with a study by Homar (2012), where lamivudine based regimen showed quicker mutations than its equivalent emtricitabine.

Findings in this study indicated that mean PDC for FDC was significantly higher than that of MDC unswitched at 6, 12 and 24 months. Subsequently viral load suppression was higher for

FDC than the MDC unswitched group at all three intervals of duration on treatment; however the difference in viral load suppression was not significant at 12 months. When also observing the proportion of participants with PDC ≥ 95% viral load suppression was higher for FDC though not significant at 12 months. There was strong positive correlation with MDC unswitched between PDC and viral Load suppression. As PDC reduced, so did viral suppression. A study conducted in Mozambique confirmed the linear correlation between adherence and viral load suppression (San Lio et al., 2008).

When comparing MDC unswitched in this study, the switched patients had better adherence and demonstrated higher viral suppression rates than MDC unswitched. These findings indicate the positive effect of switching even non-treatment naïve patients to FDC. These results were in agreement with the Armstrong et al. study conducted in Australia which found that when patients switched from multiple dose regimens to a fixed dose single pill regimen, adherence improved and viral suppression rates improved better than MDC regimens (Armstrong et al., 2015).

When compared to FDC in this study, the MDC switched group had much higher PDC values than FDC; however, the viral load suppression was surpassed by that of FDC at 6 months, while it remained similar to that of FDC at 12 and 24 months. This again indicated the positive effect FDC switches have on adherence and viral load suppression in non-treatment naïve patients (Armstrong et al., 2015). The difference in viral load suppression at 6 months could be related to the duration of the period to which the participants were on FDC as well as on the clinical profile of the participants. When observing the Cd4 count at 6 months, the MDC switched had a significantly lower mean Cd4 count than that of FDC, compromising VL suppression in spite of good adherence at 6 months.

This study found that there was a gender difference in PDC within the FDC group and not within MDC switched and MDC unswitched groups, with females demonstrating higher PDC at 6, 12 and 24 months than males, though not significant at 6 months; however this difference did not translate to improved viral load suppression for females. Females had a significantly higher viral load suppression rate than males at 6 months, but males had higher viral load suppression rates at 12 and 24 months, however this was only significant at 6 months. There was a strong negative correlation between gender and viral load suppression. A study in India could not find correlation with gender and adherence and gender and viral suppression (Shah et al. 2007). The findings in this study at 6 months, agreed with findings in a Uganda study where viral load suppression was associated with the female gender (Kipp et al. 2010), however this was not applicable at 12 and 24 months.

Immunological response in this study indicated by Cd4 count recovery from baseline, improved by more than 100% , for all the study groups, in line with expected standards of doubling the Cd4 counts after 12 months of therapy (Management of HIV/Aids, 2015). The Cd4 recovery rate was higher for MDC unswitched group than FDC at 6 and 12 months, however at 24 months Cd4 declined for MDC unswitched but remained on an up cline for FDC. The difference in mean Cd4 values at 24 months was insignificant. The increase in CD4 count for MDC unswitched could not be associated with improving VL suppression. A study in India by Pozniak et al (2006) showed that a Zidovudine fixed dose combination had a significant lower increase in Cd4 count than a multiple dose regimen and that a fixed dose combination does not necessarily result in improved clinical outcomes; the regimen make-up also contributes to clinical outcomes. In this study FDC VL suppression rates were better maintained with improving CD4 count. FDC immunological response was more in line with expected results. A study conducted in San Francisco, found that Mean VL copies were highest among the groups of people with the lowest CD4 counts, linearly decreasing as CD4 count increased (Das et al. 2010). A study by Bisson et al. (2008) indicated that Cd4 count recovery is a good predictor of viral suppression failure, and this could be related to lower viral suppression rates on MDC clients at 24 months.

Overall retention in care rate for FDC in this study was significantly higher than the MDC unswitched at 6, 12 and 24 months, but it was not different to that of MDC switched at 6 months. At 12 and 24 months the switched group had even higher retentions rates than FDC. This shows the effect of fixed dose combination on retention with the benefit of switching from multiple doses to fixed dose combination demonstrated. These results were in agreement with the Armstrong et al. study conducted in Australia which found that when patients switched from multiple dose regimens to a fixed dose single pill regimen, adherence improved better than MDC regimens (Armstrong et al., 2015). Contrary, a study conducted by Hirasen et al., in Johannesburg, South Africa found no significant difference in attrition rates between FDC and MDC at 12 months (Hirasen et al., 2017).

Death rates were significantly higher for the MDC unswitched group than FDC at 6, 12 and 24 months, with the biggest difference at 24 months (17.6% versus 4.77%). Lost to follow up where highest with the MDC unswitched group at 6 months but were higher with FDC at 12 months and with MDC switched at 24 months.

Strengths and limitations of the study

Viral load tests were not completed by clinicians timeously for all the patients retained to care according to prescribed treatment protocols. The viral load test and Cd4 count completion rates were lower than optimal ranging between 46 and 64%. The recording of the results on patients' clinical charts was also poor, but attempts were made to triangulate data from laboratory records. No other clinical files were kept in the facility. Medical information was held in patient held records that they took home. This was a gap identified with the Health patient record management systems.

Conclusion

The findings of this study showed that the fixed dose combination demonstrated better adherence at 12 and 24 months compared to multiple dose regimens. FDC demonstrated better viral suppression than multiple dose regimens at 6, 12 and 24 months. Viral load suppression for FDC was maintained at high levels close to 90% even by those patients that had less than 50% proportions of days covered on treatment, at 6 months, however VL suppression declined thereafter with these poor adherers. The impact of switching non-naïve patients from multiple to fixed dosed regimens had a positive effect on viral load suppression and on adherence. Even though the multiple dose regimen patients demonstrated higher Cd4 count recovery than FDC at 12 months, this could not be maintained at 24 months, whereas with FDC Cd4 counts continued to improve. In this study females on FDC demonstrated better adherence rates than males, but this only translated to better viral load suppression rates at 6 months. Significantly more patients were retained on the fixed dose combination than multiple dose regimens.

REFERENCES

1. Ajose O. et al., 2012. *Treatment outcomes of patients on second-line antiretroviral therapy in resource limited settings: a systemic review and meta analysis*. AIDS. 15 May 2012; 26(8): 929-38

2. Armstrong B. et al. 2015. *Single tablet regimen usage and efficacy in treatment of HIV infection in Australia*. Aids Research and Treatment. 20 September 2016.

3. Bianco J l, 2014. *Do fixed-dosed Anti-retroviral Combinations Reduce the risk of resistance?* AIDS 2014 Nov 13,28:2531

4. Bisson GP, et al. (2008*) Pharmacy Refill Adherence Compared with CD4 Count Changes for Monitoring HIV-Infected Adults on Antiretroviral Therapy*. PLoS Med 5(5): e109. https://doi.org/10.1371/journal.pmed.0050109

5. Cahn P. et al. 2014. *Dual therapy with lipinovir and ritanovir plus lamivudine versus triple therapy with lipinavir and ritanovir plus two nucleotide reverse transcriptase inhibitorsin anti-retroviral therapy naïve adults with hiv-1 infection; 48 week results of the randomised , open label , non-inferiority GARDEL trial*. Lancet Infect Dis.2014nJul 14(7): 572-80, cited by Sax P in Journal watch AIDS Clinical care.

6. Chavez JG., 2015. *CP-040 Switching to Tenofovir/Emtricitabine/ Rilpivirine in HIV -1 patients previously treated with Tenofovir/ Emtricitabine/ Efavirenz*. European Journal of Hospital pharmacy.

7. Clay P, et al. 2008. *One Pill, Once Daily: What Clinicians need to know about Atripla*. Ther Clin Risk Management, April 2008: 48(2): 291-302

8. Das M. et al., *Decreases in Community Viral Load Are Accompanied by Reductions in New HIV Infections in San Francisco.*

9. Davies, N. 2013. *Fixed-dose combination for adults accessing antiretroviral therapy* . SAJHIVMED. March 2013, Vol. 14, No. 1

10. Deeks ED, Perry C.2010.*Efavirenz/emtricitabine/tenofovir disoproxil fumarate single-tablet regimen (Atripla®): a review of its use in the management of HIV infection*. Drugs. 2010 Dec 3; 70(17):2315-38.

11. Gallant J, DeJesus E. et al. 2006. *Tenofivir DF, emtricitabine and efavirenz versus Zidovudine, lamivudine and efavirenz for HIV*. N Engl J Med 2006; 354:251-260.

12. Gallant J, et al. 2004. *Efficacy and Safety of Tenofivir DF versus Stavudine in combination therapy in anti-retroviral naïve patients: A 3 year randomised trial*. JAMA 2004: 292 (2): 191-202

13. Glanz K, et al. 2002. *Health Behaviour and Health education. Theory, research and practice.* San Fransisco: Wiley & sons.

14. Glenn D. 1992. *Determining sample size.* University of Florida

15. Guidelines for the Use of Anti-retroviral agents in HIV-1 infected Adults and Adolescent. Available ahttp://aidsinfo.nih.gov/guideless/html/1/adult-and adolescent-arv-guidelines/30/adherence, Accessed on 03 August 2016.

16. Gupta AK et al. 2010. *Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis*. Hypertension AHA 2010, Feb:55 (2): 399-407.

17. Health Belief Model: Available at htpp://www. utwente.nl/cw/theorieoverzicht/. Assessed on 12 August 2016.

18. Health Systems Trust, 2014. *The Quantitative Anti-retroviral Adherence Study in Five sites in Kwa-zulu Natal.* Available at http://www.hst.org.za. Assessed on 03 August 2016.

19. Hennekens C.2008. Fixed dose combinations. American journal of cardiovascular drugs.

20. Hicks C. 2013. *Resisting Drug Resistance in Resource –constrained Settings.* HIV/AIDS Clinical Care June 10, 2013.

21. Hingleyman L. 2016. *Atripla three times weekly maintains HIV viral suppression for 24 weeks*.HIV and hepatitis, July 2016.

22. Hirasen K. et al. 2018. *The right combination- treatment outcomes among HIV positive patients initiating first line fixed dose antiretroviral therapy in a public sector HIV clinic in Johaneesburg, South Africa*. Clinical epidermiology, 2018; 10: 17-29

23. Homar F, 2012. *Cost analysis of HIV treatment and drug-related adverse events when fixed dose combinations of antiretrovirals were stopped, versus continuation with FDC'.s*. Health Econ Rev, 2012:2;16, Sep 2012.

24. Integrated Chronic Disease Management Guidelines, 2014. Available at htpp://www.health.vic.gov.au/phc/icdm.

25. Kader R, Seedat S. 2014. *Hazardous and Harmful use of alcohol and/ or other Drugs and Health status Among South African Patients attending HIV Clinics*. AIDS and Behaviour 18.3 : 524-34

26. Keith H. 2014. citing Chow E et al.*Cd4 cell counts rarely Needed in Patients doing well on ART*. HIV Med 2014 Sep 18.

27. Keith H.2014. *Incomplete Adherence Linked to greater Risk for Residual Low level Viremia.* AIDS 2014 Jan 14; 28:181

28. Kipp W., et al., 2010. *Gender differences in antiretroviral treatment outcomes of HIV patients in rural Uganda.* AIDS Care, 2010 March; 22(3): 271-8

29. Khopotso B. 2012. Simplifying Aids *Treatment*. The centre for the study of Aids, Dec 2012, 20:05.

30. Kling J. 2014. *Once daily Combo outperforms Twice daily in COPD*. Available at http://www.medscape.com. American College of physicians, Oct 2014. Assessed on 09 November 2014.

31. Marconi V. 2013. *How early should we start treatment?* Plos Med 103 Dec 10: 31001568

32. Marconi V. 2014. *Early Warning Indicators for Virological failure in the Southern African Context.* AWACC Conference 2014.

33. Marconi Vet al .2008. *Prevalence of HIV-1 drug resistance after failure of a first highly active anti-retroviral therapy regimen in Kwazulu natal. South Africa*. Available at www.reserachgate.net/piblication. Accessed on 15 October 2016.

34. Martinez-Picado J. et al., 2016. *Persistent HIV-1 replication during antiretroviral therapy.* Curr Opin HIV AIDS. 2016 July: 11(4): 417-423

35. Melaku A Eyassu, 2016. Adherence to antiretroviral therapy among HIV and AIDS patients at the Kwa-Thema clinic in Gauteng Province, South Africa. African Journal of primary health care & family medicine: 8(2), 1-7, 2016.

36. Messerli FH. 2007. Fixed dose combinations improve medication compliance: a meta analysis. American Journal of Med : 120 (8): 173-9

37. Muller A. et al., 2011. *Potential Pharmacokinetic Interactions between anti-retroviral and medicinal plants used as complementary and African traditional medicines.* Biopharmaceutics and Drug Disposition Vol 32, pages 458-470, Nov 2011.

38. Nigori R, et al. 2012. *Pharmacokinetic profiling of efavirenz-emtricitabine-tenofovir fixed dose combination in pregnant and non-pregnant rats*. Biopharm Drug Dispos. 2012 Jul;33(5):265-77. doi: 10.1002/bdd.1794. Epub 2012 Jun 2

39. Olawale A. et al. 2012. *Treatment Outcomes of patients on second-line anti-retroviral therapy in resource-limited settings; a systematic review and meta- analysis.* AIDS 2012,26

40. Orom, H , Homish DL, Homish, GG. 2014. *Quality of physician-patient relationships is associated with the influence of physician treatment recommendations among patients with prostate cancer who chose active surveillance*. Urologic Oncology [2014, 32(4):396-402]

41. Parry C. 2014. *Hazardous and harmful use of alcohol and / or other drugs and Health status among South African patients Attending HIV clinics.* Aids and Behaviour 18.3 (Mar 2014: 525-34.

42. Pozniak A, Gallant J, et al. 2006.*TenofovirDF,Emtricitabine, and Efivarenz versus Fixed dose Zidovudine/ Lamivudine and Efivarenz in Anti-retroviral – Naïve Patients: Virological, Immunological, and Morphologic Changes- a 96 week analysis*. J. Acquired Immunine Defeciency syndrome: 2006; 4395): 535-540.

43. Pujari, S. 2008.*Effectiveness and safety of generic fixed-dose combination of tenofovir/ emtricitabine/ efavirenz in HIV-1-infected patients in Western India.* Medscape journal of medicine 10.8(2008): 196.

44. San Lio MM, et al., 2008. *Evaluating adherence to highly active antiretroviral therapy with use of pill counts and viral load measurement in the drug resources enhancement against AIDS and malnutrition program in Mozambique*. Clinical Infectious Diseases, Volume 46, Issue 19. 15 May 2008, pages 1609-1616

45. Serebruany V. , 2008. *Bleeding risks of combination vs single antiplatelet therapy: a meta-analysis of 18 randomised trials.* Findamental and clinical pharmacology, Vol 22, issue 3. 15 May 2008

46. Shah B et al., 2007. Adherence to Antiretroviral Therapy and Virologic Suppression among HIV-Infected Persons Receiving Care in Private Clinics in Mumbai, India . Clinical Infectious Dieseases Vol 44: 1 May 2007

47. Sharp, M.2006. *Application for inclusion of efivarenz, emtricitabine and tenofivir disoproxil fumarate Fixed dose Combination tablets* on the WHO Model List of Essential Medicines

48. Steel G. et al., 2007. *Development of a Multi-Method Tool to measure ART Adherence in Resource –Constrained Settings: The South Africa Experience*. Rational Pharmaceutical Management Plus Program. Management Sciences for Health.

49. Stone VE et al. 2001. *Antiretroviral Regimen Complexity, Self-Reported Adherence, and HIV Patients' Understanding of their regimens: Survey of Women in the HER Study*. Journal of Acquired Immune Deficiency Syndromes: October1, 2001.

50. Stone VE, 2001.*Strategies for Optimizing Adherence to Highly Active Antiretroviral Therapy: Lessons from Research and Clinical Practice*. Oxford Journals, Medicine, Clinical Infectious Diseases, Volume 33, Issue 6, 865-872.

51. Suarez-Garcia I et al.2014. *Compliance with HIV Treatment Guidelines and Its effect on Outcomes*. HIV Med 2014 Feb 15:86

52. Thompson M, et al. 2012. *Guidelines for improving entry into and retention in careand anti-retroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel*. Ann Intern Med, 2012, Jun 5; 156 (11)

53. WHO .2012. *Pharmacological equivalence and Clinical Interchangeability of Lamivudine and Emtricitabine: A Review of Current Literature*.

CHAPTER 4 – SYNTHESIS CHAPTER

4. 1 Impact of FDC on adherence

Only a few years are left before all countries are to meet the Vision 90-90-90 targets and yet only a few countries have achieved those, and South Africa is not there yet. According to Marconi V, 2013, South Africa is reporting low levels of virologic failure but the challenge is to maintain those low levels. It therefore remains critical that patients must remain virally suppressed and as many factors contribute to non-adherence, the introduction of fixed dose regimen is only bit one of the strategies of improving adherence. The results from the first study indicated that better adherence was achieved with the fixed dose combination compared to those of multiple dose regimens but the levels of 65% of absolute adherence at 6 months are far from being optimal. At 24 months absolute adherence for FDC was 50% and that of MDC was 23.3%. The adherence curve theory by Friedland states that at around 21 weeks a patients motivation to taking their medication plateaus, this study is in agreement with that theory as soon after 6 months the adherence levels dropped, even for these patients that need to be on ART for life.

The FDC was not able to bridge the differences in adherence between females and males. Of interest findings from his study indicated that females had the lowest adherence rates on MDC unswitched regimen than males at 6 months contrary to previous studies conducted in SA (Melaku et al., 2016) and in India (Shah et al., 2007). With FDC females demonstrated better adherence than males. This suggests that females may be more compromised than males in taking more complex regimens, especially early on in treatment. This needs further investigation. Marconi in 2013 also noted this phenomenon where females did not do well as expected, where he identified that women experienced more ARV related adverse drug reactions (ADR's) than males. This study's limitation was that it was not able to evaluate the impact of FDC on reducing drug toxicities, due to the fact that recording of clinical notes on patients charts was not optimal. This factor on its own could also indicate that side effects on FDC and on MDC might not have been properly managed if not documented. Side effects and ADR's contribute to non-adherence to treatment even on FDC (Pujari,2008, and Chavez, 2015). Other strategies other than regimen simplication have to be adopted to maintain optimal viral suppression. Strategies to address socioeconomic factors, access to health facilities, health system factors, gender adherence gaps all will have an impact on improving the life of people living with HIV Aids and the community at large (Marconi V, 2014).

4.2 The effect of switch to FDC for non -treatment naïve patients on adherence

Results from this study suggested that patients that were previously on MDC then switched to FDC demonstrated better proportion of days covered and absolute adherence (at 12 and 24 months) than those patients that were treatment naïve on FDC. The level of adherence for this group was almost constant over time, indicating low decline from 6 months to 24 months. Armstrong in 2015 also demonstrated the benefit of switching non-naïve patients to fixed dose regimens. However since the regimen switched to was the same as FDC regimen there must be other factors contributing to better performance. These reasons for switch according to the SA ART guidelines were for changing patients that were previously on known toxic regimens, for an example Stavudine based, and for reducing pill load for patients who were virally suppressed. These patients were already experienced on more complex regimens. At 6 months this study could not find significant differences in absolute adherence between those on MDC unswitched (64.7%) and FDC (65.5%), meaning these clients were already having similar levels of adherence early on in treatment, but being provided with even a simpler regimen would make them more capable of demonstrating even better adherence rates when a new simpler regimen was introduced. The motivation factor that wanes after 6 months, explained by the adherence curve theory would be applicable to FDC group, but not on those patients starting a new regimen. Motivational enhancement therapy as used in most addiction treatment regimens (Holt, 2006), works on the premise that access to treatment is never adequate (Centre on addiction, 2017) but constant motivation and treatment support is needed for these patients that often relapse, that should be tailor made to address individuals needs including management of side effects. Enrolment of ART patients onto enhanced adherence clubs should be encouraged even for those patients not classified as defaulters.

4.3 Impact of FDC on Viral Load suppression

This study was able to demonstrate that even with less than optimum adherence levels, the Tenofovir/ emtricitabine/ efavirenz FDC regimen was able to achieve high viral load suppression rates up to 24 months. After 6 months the MDC switched group also demonstrated similar viral load suppression rates. The results indicate the positive benefits of using a fixed dose combination regimen on virologic response. Marconi, 2013 suggests that virologic response is an early warning indicator that can used to predict viral failure, and that it can be a measure of adherence. The study was able to confirm the positive strong correlation that exist between adherence and viral load suppression with FDC, significant at 0.01 level (2 tailed), however at 24 months this correlation was not significant. As VL suppression improved adherence was not improving proportionally. Therefore one can argue if viral load suppression can be used as an indicator of adherence for this regimen. Hingleyman (2016) proposes that taking the Tenofovir/ emtricitabine/ efavirenz FDC

regimen three times a week instead of daily can still maintain adequate VL suppression, but this is only applicable for patients already VL suppressed. This could have benefits of reducing the pill burden further. This study was able to demonstrate that patients with PDC below 50% were still able to achieve 93% VL suppression even at these low levels of adherence, in support of Hingleymans findings. However the study found that at 12 months, with these poor adherers VL suppression dropped to 56%. The practice of reducing the dosing frequency of FDC cannot be applicable to all patients, this could only be explored with only those clients with proven good adherence, above 95%, to reduce probability of side effects. In females the higher adherence levels achieved on FDC compared to males could not translate to better viral load suppression; negative correlation was found. Other factors other than adherence could contribute to this as proposed by Marconi (2013), such as ADRs, unsafe sex practices, depression that could be significant as contributing factors to viral failure.

Resistance to antiviral therapy is the limiting factor in the management of patients with HIV. These viral mutations are more associated with low adherence to treatment. K65R mutation is rarely selected (1.7–4%) with tenofovir disoproxil fumarate (TDF) and abacavir (ABC), as compared with the high incidence (>40%) of thymidine analog mutations associated with zidovudine based regimens. TDF/emtricitabine and ABC/lamivudine (ABC/3TC) combinations are recommended due to the high barrier to the development of K65R mutations. There is also low–intermediate level profile of cross-resistance conferred by K65R to TDF, ABC and 3TC. 3TC/emtricitabine-associated M184V mutations. The results have suggested that combination antiretroviral therapy (ART) have resulted in better maintenance of viral load suppression and led to marked decreases in mortality. The failure to suppress viral replication during therapy leads to the selection and expansion of drug-resistant viruses. A study done by Brenner et al, in 2009, found similar results where there was high resistance to TDF based viral mutations in ART patient naïve patients.

4.4 Impact of FDC on Immunologic response and death rates

Cd4 count recovery was higher for MDC at 12 months, but the immunologic recovery was more sustained with FDC. Homar (2008) argues that by 24 weeks plasma viral load is suppressed to levels below 100 copies, but there is usually a delayed immune recovery, followed by a sustained increase over time. Cd4 count for FDC improved in spite of reduced adherence rates at 24 months. Cd4 count for MDC dropped at 24 months, and VL suppression also dropped to 56%. Cd4 count can be used to detect viral failure (Bisson, 2008) but this is not as accurate as using pharmacy records as measure of adherence (Marconi, 2013). Poor Immunologic response is correlated to

poor clinical outcomes (Castro, 2005). This was confirmed by higher death rates with MDC compared to FDC.

4.5 General Conclusion

This study was able to demonstrate that introduction of the fixed dose regimen was a good strategy to improve adherence levels, viral load suppression and immunologic response on ART. However the adherence levels were still lower than the optimal levels which might compromise care later on in treatment. The fixed dose combination regimen introduced was able to demonstrate good viral load suppression rates even in patients with 50% adherence at 6 months, indicating potency of the regimen. The study was only restricted to 24 months and no conclusive evidence could be demonstrated to show that as adherence reduced with time to levels below fifty percent, viral load suppression could still be maintained thereafter. What was evident from this study was that for those patients on FDC who had proportion of days covered on treatment less than fifty percent, beyond 6 months, viral load suppression almost halved, suggesting that additional strategies need to be adopted to further improve adherence. Switching of non-treatment naïve patients to FDC should be done more promptly. More adherence support needs to be provided to males to improve adherence.

4.6 Recommendations for Future Research

Future research should investigate the impact of side effects and adverse drug reactions of the tenofovir/ emtricitabine/ efavirenz based fixed dose regimen as a factor for non-adherence as this study identified a gap on the management of drug side effects and ADR's. Further investigations need to be done on factors contributing to reduced viral load in females in spite of them having adherence rates than males. Further research needs to be conducted on the effectiveness of the FDC on viral load suppression when taken only three times a week as Hingleyman's study proposes before 6 months and results of good suppression suggest from this study, as an alternative to managing side effects early on in ART treatment.

REFERENCES

1. Armstrong B. et al. 2015. *Single tablet regimen usage and efficacy in treatment of HIV infection in Australia*. Aids Research and Treatment. 20 September 2015.

2. Bisson GP, et al. (2008*) Pharmacy Refill Adherence Compared with CD4 Count Changes for Monitoring HIV-Infected Adults on Antiretroviral Therapy*. PLoS Med 5(5): e109. https://doi.org/10.1371/journal.pmed.0050109

3. Castro A (2005) *Adherence to antiretroviral therapy: Merging the clinical and social course of AIDS.* PLoS Med 2(12): e338.

4. Chavez JG., 2015. *CP-040 Switching to Tenofovir/Emtricitabine/ Rilpivirine in HIV -1 patients previously treated with Tenofovir/ Emtricitabine/ Efavirenz*. European Journal of Hospital pharmacy.

5. *The importance of treatment motivation*: https//www.centreonaddiction.org, 11 July 2017

6. Friedland G et al., 1999. *Attaining higher goals in HIV treatment: the central importance of adherence*. AIDS 1999

7. Hingleyman L. 2016. *Atripla three times weekly maintains HIV viral suppression for 24 weeks*.HIV and hepatitis, July 2016.

8. Halt W, 2006.*The concept of Motivation for treatment.* The American Journal of psychiatry. 1 April 2006.

9. Homar F, 2012. *Cost analysis of HIV treatment and drug-related adverse events when fixed dose combinations of antiretrovirals were stopped, versus continuation with FDC'.s*. Health Econ Rev, 2012:2;16, Sep 2012

10. Homer L. et al.,2008. *Effect of Highly Active Antiretroviral Therapy on Viral Burden in the Lungs of HIV-Infected Subjects*. *The Journal of Infectious Diseases*, Volume 197, Issue 1, 1 January 2008.

11. Marconi V. 2013. *How early should we start treatment?* Plos Med 103 Dec 10: 310015

12. Marconi V. 2014. *Early Warning Indicators for Virological failure in the Southern African Context.* AWACC Conference 2014.

13. Melaku A Eyassu, 2016. *Adherence to antiretroviral therapy among HIV and AIDS patients at the Kwa-Thema clinic in Gauteng Province, South Africa*. African Journal of primary health care & family medicine: 8(2), 1-7, 2016.

14. Pujari S. 2008. *Effectiveness and safety of generic fixed-dose combination of tenofovir/ emtricitabine/ efavirenz in HIV-1-infected patients in Western India.* Medscape journal of medicine 10.8(2008): 196.

15. San Lio MM, et al., 2008. *Evaluating adherence to highly active antiretroviral therapy with use of pill counts and viral load measurement in the drug resources enhancement against AIDS and malnutrition program in Mozambique*. Clinical Infectious Diseases, Volume 46, Issue 19. 15 May 2008, pages 1609-1616

16. Shah B et al., 2007. *Adherence to Antiretroviral Therapy and Virologic Suppression among HIV-Infected Persons Receiving Care in Private Clinics in Mumbai, India* . Clinical Infectious Dieseases Vol 44: 1 May 2007

17. Sharp, M.2006. *Application for inclusion of efivarenz, emtricitabine and tenofivir disoproxil fumarate Fixed dose Combination tablets* on the WHO Model List of Essential Medicines

Appendices

Appendix 1: BREC approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

11 February 2016

Mrs L Jali Lubanga
Pharmacology
School of Health Sciences
lulujali@yahoo.com

Protocol: Comparison of adherence to treatment, safety and effectiveness of fixed dose combination ARV drugs to multiple dose regimens in adult patients in public sector.
Degree: MSc
BREC reference number: BE084/15

EXPEDITED APPLICATION

The Biomedical Research Ethics Committee has considered and noted your application received on 24 March 2015.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 22 January 2016 to queries raised on 24 December 2015 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 **11 February 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 **08 March 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: Nkosto@ukzn.ac.za
cc postgrad: nenep1@ukzn.ac.za

Biomedical Research Ethics Committee
Professor J Tsoka-Gwegweni (Chair)
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Appendix 2: Approval from Kwa Zulu Natal provincial Department of Health

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

330 Langalibalele street.
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DIRECTORATE:
Health Research & Knowledge Management (HKRM)

Reference: **HRKM283/15**
KZ_2015RP30_720

Date: 14 October 2015

Dear Ms H L Jali-Lubanga

Subject: Approval of a Research Proposal

1. The research proposal titled **'Comparison of Adherence to treatment, safety and effectiveness of Fixed Dose combination ARV drugs to multiple dose regimens in adult patients in public sector'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at the selected facilities at Uthukela District.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Ms G Khumalo on 033-395 3189.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 14/10/15

Fighting Disease. Fighting Poverty. Giving Hope

Appendix 3: Approval from uThukela Health District

health

Department:
Health
PROVINCE OF KWAZULU-NATAL

UTHUKELA DISTRICT
60A Midblock, Corner Alexander Street,
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www.kznhealth.gov.za

18 November 2014

Mrs Helen Lulama Jali-Lubanga

RE: APPLICATION FOR SUPPORT TO CONDUCT A STUDY IN UTHUKELA HEALTH FACILITIES

Please be informed that I have acknowledged your request for conducting research on **"Comparison of Adherence to treatment, safety and effectiveness of Fixed Dose combination Anti-Retroviral drugs to multiple dose regimens in adult patients in public sector"** in UThukela Health facilities.

Please note the following:

1. Your letter received on 17 November 2014 refers.
2. Uthukela District must ensure adherence to all the policies, produces, protocols and guidelines of the Department of Health with regards to this research.
3. Your research will only commence once this office has received confirmation of the approval by HOD from the provincial Health Research Committee in the KZN Department of Health.
4. However your research is hereby supported.
5. I trust that you will find all to be in order.

Yours faithfully

MRS M T ZULU
DISTRICT MANAGER
UTHUKELA HEALTH DISTRICT

Appendix 4 : Letters of support from health care facilities

To: The Clinical Manager
Indaka Health Sub-District
St Chads CHC

From: Lulama Jali-Lubanga
UKZN Student no- 993241127

Date: 02 June 2015

Dear Dr. R. Okafor,

RE: Request for approval to conduct a study in 1 of your facilities at St Chads CHC

I am a part-time student at the University of Kwa Zulu Natal, studying towards a Master's degree in Pharmacy. As part of the fulfilment of requirements for the degree with the University of KwaZulu-Natal; I have submitted my research proposal to BREC in March 2015 and as part of the requirements for the application I request your permission and support to conduct this study in the facilities under your responsibility. The title of the study is "***Comparison of Adherence to treatment, safety and effectiveness of Fixed Dose combination Anti- Retroviral drugs to multiple dose regimens in adult patients in public sector***"

The objectives of the study are to:

1. To establish whether the fixed dose combination formulation and the resultant reduced pill load result in better adherence to ARV treatment than multiple dose regimens.
2. To determine whether patients on FDCs have better clinical outcomes than those on multiple dose antiretroviral regimens.
3. To establish any other factors other than the drug administration dosage form that contributes to non-adherence to antiretroviral treatment among HIV positive patients.

The study will be conducted 4 other sites at Uthukela District.

The main Benefits of the study for the Community of Uthukela are:

A. Identification of factors affecting adherence for patients on both Fixed Dose combination and multiple dose ART regimens, so as to advise on Health District systems that can be utilised to retain patients to care for ultimate improved morbidity and mortality related to HIV/AIDS
B. Identification of side effects that patients might experience on the both treatment regimens so that they receive individualised care.
C. The study will also provide an opportunity for pharmacists, nurses and CCG's working at Uthukela to learn from Pharmacovigilance practices that might be adopted from the study.

A copy of the Research proposal is herewith attached, and an information sheet about the study participants is attached to this letter. I intend to conduct a survey among 500 randomly selected HIV patients attending the antiretroviral site in the above mentioned facilities. For this I request your assistance and permission in order to conduct this research, on days that I will have taken as leave from work.

This study will be fully approved by a review committee of the School of Health Sciences before the commencement of the study. This project is fully registered with the postgraduate office of School of Health Sciences, Westville Campus/UKZN. You may contact Ms Phindile Nene at the research office

REQUEST FOR APPROVAL TO CONDUCT RESEARCH TOWARDS A MASTERS IN PHARMACY DEGREE

(telephone: 031 260 8280) and my supervisor Mr Manimbulu Nlooto, (telephone: 031 260 7030, email: Nlooto@ukzn.ac.za) in the Discipline of Pharmaceutical sciences for further clarity.

Hoping this receives your kind consideration

Yours faithfully.

Mrs. Lulama Jali-Lubanga

02/06/2015
Date

APPROVED/ ~~NOT~~ APPROVED

Dr. R. Okafor
Clinical Manager
Indaka Health Sub-District
St Chads CHC

03/06/2015
Date

To: The Clinical Manager
Okhahlamba Health Sub-District
Emmaus

From: Lulama Jali-Lubanga
UKZN Student no- 993241127

Date: 02 June 2015

Dear Dr. Kekana

RE: Request for approval to conduct a study in 2 of your facilities at Okhahlamba Sub-district

I am a part-time student at the University of Kwa Zulu Natal, studying towards a Master's degree in Pharmacy. As part of the fulfilment of requirements for the degree with the University of KwaZulu-Natal; I have submitted my research proposal to BREC in March 2015 and as part of the requirements for the application I request your permission and support to conduct this study in the facilities under your responsibility. The title of the study is "***Comparison of Adherence to treatment, safety and effectiveness of Fixed Dose combination Anti- Retroviral drugs to multiple dose regimens in adult patients in public sector***"

The objectives of the study are to:

1. To establish whether the fixed dose combination formulation and the resultant reduced pill load result in better adherence to ARV treatment than multiple dose regimens.
2. To determine whether patients on FDCs have better clinical outcomes than those on multiple dose antiretroviral regimens.
3. To establish any other factors other than the drug administration dosage form that contributes to non-adherence to antiretroviral treatment among HIV positive patients.

The sites where the study will be conducted are: Emmaus Hospital and a down referral site at Isibane in Winterton, (a similar study will be conducted in 5 other sites at Uthukela District.)

The main Benefits of the study for the Community of Uthukela are:

A. Identification of factors affecting adherence for patients on both Fixed Dose combination and multiple dose ART regimens, so as to advise on Health District systems that can be utilised to retain patients to care for ultimate improved morbidity and mortality related to HIV/AIDS
B. Identification of side effects that patients might experience on the both treatment regimens so that they receive individualised care.
C. The study will also provide an opportunity for pharmacists, nurses and CCG's working at Uthukela to learn from Pharmacovigilance practices that might be adopted from the study.

A copy of the Research proposal is herewith attached, and an information sheet about the study participants is attached to this letter. I intend to conduct a survey among 500 randomly selected HIV patients attending the antiretroviral site in the above mentioned facilities. For this I request your assistance and permission in order to conduct this research, on days that I will have taken as leave from work.

This study will be fully approved by a review committee of the School of Health Sciences before the commencement of the study. This project is fully registered with the postgraduate office of School of Health Sciences, Westville Campus/UKZN. You may contact Ms Phindile Nene at the research office (telephone: 031 260 8280) and my supervisor Mr Manimbulu Nlooto, (telephone: 031 260 7030, email: Nlooto@ukzn.ac.za) in the Discipline of Pharmaceutical sciences for further clarity.

REQUEST FOR APPROVAL TO CONDUCT RESEARCH TOWARDS A MASTERS IN PHARMACY DEGREE

Hoping this receives your kind consideration

Yours faithfully

Mrs. Lulama Jali-Lubanga — 02/06/2015 Date

APPROVED/ ~~NOT APPROVED~~

Dr. M. Kekana
Clinical Manager
Okhahlamba Health Sub-District
Emmaus

31.07.2015 Date

To: The Clinical Manager
Estcourt Health Sub-District
Estcourt

From: Lulama Jali-Lubanga
UKZN Student no- 993241127

Date: 02 June 2015

Dear Dr. P. Kande

Request for approval to conduct a study in 3 of your facilities at Estcourt Sub-district

I am a part-time student at the University of Kwa Zulu Natal, studying towards a Master's degree in Pharmacy. As part of the fulfilment of requirements for the degree with the University of KwaZulu-Natal; I have submitted my research proposal to BREC in March 2015 and as part of the requirements for the application I request your permission and support to conduct this study in the facilities under your responsibility. The title of the study is "***Comparison of Adherence to treatment, safety and effectiveness of Fixed Dose combination Anti- Retroviral drugs to multiple dose regimens in adult patients in public sector***"

The objectives of the study are to:

1. To establish whether the fixed dose combination formulation and the resultant reduced pill load result in better adherence to ARV treatment than multiple dose regimens.
2. To determine whether patients on FDCs have better clinical outcomes than those on multiple dose antiretroviral regimens.
3. To establish any other factors other than the drug administration dosage form that contributes to non-adherence to antiretroviral treatment among HIV positive patients.

The sites where the study will be conducted are: Injisuthi Clinic, Wombezi Clinic and at the Injisuthi Down referral site (a similar study will be conducted in 5 other sites at Uthukela District.)

The main Benefits of the study for the Community of Uthukela are:

A. Identification of factors affecting adherence for patients on both Fixed Dose combination and multiple dose ART regimens, so as to advise on Health District systems that can be utilised to retain patients to care for ultimate improved morbidity and mortality related to HIV/AIDS
B. Identification of side effects that patients might experience on the both treatment regimens so that they receive individualised care.
C. The study will also provide an opportunity for pharmacists, nurses and CCG's working at Uthukela to learn from Pharmacovigilance practices that might be adopted from the study.

A copy of the Research proposal is herewith attached, and an information sheet about the study participants is attached to this letter. I intend to conduct a survey among 500 randomly selected HIV patients attending the antiretroviral site in the above mentioned facilities. For this I request your assistance and permission in order to conduct this research, on days that I will have taken as leave from work

This study will be fully approved by a review committee of the School of Health Sciences before the commencement of the study. This project is fully registered with the postgraduate office of School of Health Sciences, Westville Campus/UKZN You may contact Ms Phindile Nene at the research office

REQUEST FOR APPROVAL TO CONDUCT RESEARCH TOWARDS A MASTERS IN PHARMACY DEGREE

(telephone: 031 260 8280) and my supervisor Mr Manimbulu Niooto, (telephone: 031 260 7030, email: Niooto@ukzn.ac.za) in the Discipline of Pharmaceutical sciences for further clarity.

Hoping this receives your kind consideration

Yours faithfully,

Mrs. Lulama Jali-Lubanga

02/06/2015
Date

APPROVED/ NOT APPROVED

Dr. [illegible]. Kande
Acting Clinical Manager
Estcourt Health Sub-District
Estcourt

28/07/2015
Date

To: The Chief Executive Officer
Emnambithi Health Sub-District
C/O Ladysmith Hospital
Ladysmith

From: Lulama Jali-Lubanga
UKZN Student no- 993241127

Date: 02 June 2015

Dear Dr. R. Moeketsi

Request for approval to conduct a study in 2 of your facilities at Emnambithi Sub-district

I am a part-time student at the University of Kwa Zulu Natal, studying towards a Master's degree in Pharmacy. As part of the fulfilment of requirements for the degree with the University of KwaZulu-Natal; I have submitted my research proposal to BREC in March 2015 and as part of the requirements for the application I request your permission and support to conduct this study in the facilities under your responsibility. The title of the study is "***Comparison of Adherence to treatment, safety and effectiveness of Fixed Dose combination Anti- Retroviral drugs to multiple dose regimens in adult patients in public sector***"

The objectives of the study are to:

1. To establish whether the fixed dose combination formulation and the resultant reduced pill load result in better adherence to ARV treatment than multiple dose regimens.
2. To determine whether patients on FDCs have better clinical outcomes than those on multiple dose antiretroviral regimens.
3. To establish any other factors other than the drug administration dosage form that contributes to non-adherence to antiretroviral treatment among HIV positive patients

The sites where the study will be conducted are: Ladysmith Hospital and at Driefontein Clinic(a similar study will be conducted in 5 other sites at Uthukela District.)

The main Benefits of the study for the Community of Uthukela are:

A. Identification of factors affecting adherence for patients on both Fixed Dose combination and multiple dose ART regimens, so as to advise on Health District systems that can be utilised to retain patients to care for ultimate improved morbidity and mortality related to HIV/AIDS
B. Identification of side effects that patients might experience on the both treatment regimens so that they receive individualised care.
C. The study will also provide an opportunity for pharmacists, nurses and CCG's working at Uthukela to learn from Pharmacovigilance practices that might be adopted from the study.

A copy of the Research proposal is herewith attached, and an information sheet about the study participants is attached to this letter. I intend to conduct a survey among 500 randomly selected HIV patients attending the antiretroviral site in the above mentioned facilities. For this I request your assistance and permission in order to conduct this research, on days that I will have taken as leave from work.

This study will be fully approved by a review committee of the School of Health Sciences before the commencement of the study. This project is fully registered with the postgraduate office of School of Health Sciences, Westville Campus/UKZN. You may contact Ms Phindile Nene at the research office

REQUEST FOR APPROVAL TO CONDUCT RESEARCH TOWARDS A MASTERS IN PHARMACY DEGREE

(telephone 031 260 8280) and my supervisor Mr Manimbulu Niooto. (telephone 031 260 7030, email Nicoto@ukzn.ac.za) in the Discipline of Pharmaceutical sciences for further clanty

Hoping this receives your kind consideration

Yours faithfully

Mrs. Lulama Jali-Lubanga

02/06/2015
Date

APPROVED/ NOT APPROVED

Dr. R. Moeketsi
Chief Executive Officer
Emnambithi Health Sub-District
Ladysmith

16/07/2015
Date

Appendix 5: Information Sheet about the study

You will be enrolled in the study for a period of 12 months where your body's response to medication will be monitored by the nurses at the clinic by evaluating how your Cd4 improves and how the virus in the body is suppressed.

The information you provide will assist the department of health to identify any problems that patients experience at home, as well as when they come to the health facilities. It will assist to better understand some of the unwanted effects combination or single ARV medicines might have.

This information will be treated with the utmost confidentiality, and no names of patients will be recorded and only a code will be used as your identifier, and the information will be stored in a lockable computer. After the study is completed the information will be destroyed. Participants will be required to attend the clinic regularly, and to bring back all their medication every time they visit the clinic or hospital in the first 6 months of the study. The researchers will ensure that you are not treated any differently to normal procedure conducted at the facility, and you will be requested to come to the clinic to have your bloods taken normally like everyone else.

You will be given an opportunity to ask questions throughout the whole process. Whenever you feel uncomfortable about any of the procedures, you will be welcome to exit the study, and will not be obliged to participate further

The study may involve the following discomforts.
You will be expected to spend about 20 more minutes than normal, to answer a questionnaire. If it has been found that you have not been able to attend your clinic regularly, a community care giver may visit your home to ensure that you are counselled and brought back o care to maintain your health.

We hope that the study will provide you with an opportunity to be better supported with your treatment and selection of medication that better suits you as an individual. If you happen to experience side effects on the medication you were started on, you will be referred to a clinician who will evaluate you and provide care for you so that you do not experience that again.

You will however not receive monetary compensation by being involved in the study. Participation is voluntary.

This study has been ethically reviewed and approved by the UKZN Biomedical research Ethics Committee (approval number_____).

In the event of any problems or concerns/questions you may contact the researcher at (provide contact details) or the UKZN Biomedical Research Ethics Committee, contact details stated as follows:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

unwanted effects of the medication that you have had.

Appendix 6: Consent form

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

I (Name),..... have been informed about the study entitled : ***Comparison of Adherence to treatment, safety and effectiveness of Fixed Dose combination Anti- Retroviral drugs to multiple dose regimens in adult patients in public sector;***

conducted by Mrs HL Jali-Lubanga/ or research assistant .....

I understand the purpose and procedures of the study. I understand that I will be giving consent to be interviewed by the researcher or assistants and answer to questions that are related to taking of my anti-retroviral medicines. I consent to bring any medication that I might have at home for the medication to be evaluated. In case where problems have been identified with adherence to treatment or to the way my body responds to treatment, I consent to have the researcher sharing this information with the nurses and doctors working in the clinic I am attending, for me to get additional help;or to be referred to an adherence counselor. I understand that the information I provide will be treated with the utmost confidentiality.

I have been given an opportunity to answer questions about the study and have had answers to my satisfaction.

I declare that my participation in this study is entirely voluntary and that I may withdraw at any time without affecting any treatment or care that I would usually be entitled to.

I have been informed that there will be no monetary compensation for participation in the study.

If I have any further questions/concerns or queries related to the study I understand that I may contact the researcher at (0719857982).

If I have any questions or concerns about my rights as a study participant, or if I am concerned about an aspect of the study or the researchers then I may contact:

---------- ----------
Signature of Participant Date

---------- ----------
Signature of Witness Date

---------- ----------
Signature of Translator Date

Statement by the researcher/person taking consent

I have to the best of my ability made sure that the participant understands that the point of the research and what it entails. I confirm that the participant was given an opportunity to ask questions

about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily. A copy of this Informed Consent Form has been provided to the participant.

Signature of the person taking the consent----------**Date**----------

Signature of Researcher or person giving the consent form---------- **Date**----------

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

Appendix 7: Adherence data extraction sheet

APPENDIX 7: DATA COLLECTION SHEET: ADHERENCE

FDC FILES at 6 months

Facility Name :

ADHERENCE COLLECTION FORM Date:

Prescription code	Date of Birth	GENDER	Patient Starting regimen	ART Start Date	Age in years at start of ART	New Regimen	Date of change	Period of previous	Review 84 days	No of days in period	No of days missed 4-6 months	No of days Covered	PDC (%)	Adherent (>95%) Y=1, N=0

Appendix 8: Data collection form clinical outcomes

APPENDIX 8 Data Collection Form- Clinical Data

Data Collection Form- Fixed Dose Combination TDF/3TC/EFV Regimen (6 months)

Name of Data Collector:..... Facility Name:.....

Rx	Prescription code	Age	Gender		Patient regimen	ART Start Date	3 months							6 months								
			F	M			Creatinine level	Side Effects / ADR reported Y/N	Presence of OI	Other abnormal lab results		Clinical Outcome Rx/D/LTF		Creatinine level	Side Effects / ADR reported	Presence of OI	Other abnormal lab results	Viral Load suppressed Y/N		Clinical Outcome Rx/D/LTF	
									Y	N						Y	N			Y	N
1																					
2																					
3																					
4																					
5																					
6																					
7																					
8																					
9																					
10																					
	Total																				

Date:..... Sheet No: .....