Incidence and Prevalence Of Renal Dysfunction In Antiretroviral Therapy (ART) Naïve Patients Starting A Tenofovir (TDF) Based ART Regimen In Mitchell's Plain Community Health Centre (CHC) ARV Clinic

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DECLARATION

I, Dr Olanrewaju Philips Fayanju, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Title: Incidence and Prevalence of Renal Dysfunction In Antiretroviral Therapy (ART) Naïve Patients Starting A Tenofovir (TDF) Based ART Regimen In Mitchell's Plain Community Health Centre (CHC) ARV Clinic.

Background: Tenofovir disoproxil fumarate (TDF) has high antiretrovirus (ARV) activity and available in fixed dose combination (FDC). However, it has been found to cause renal dysfunction.

Objectives: To document the prevalence, incidence, pattern of occurence and associated factors of nephrotoxicity in patients initiated on TDF based ART regimen in Mitchell's Plain CHC ARV Clinic and make recommendations.

Methodology: The study was conducted by reviewing retrospective records of all ARV naïve HIV positive adults initiated on TDF based ARV regimen from January 2016 to June 2016. The creatinine clearance (CrCl) was calculated from follow up parameters till June 2018.

Results: 87 patients were included in the study and 56% were female. The mean age was 34 years. Majority, 83%, had normal renal function at ART initiation. Older age [OR = 1.11; 95% CI (1.03–1.19), p =0.005], was associated with an increased probability of non-normal renal function at baseline. The incidence of CrCl < 90ml/min were 1.5% at 1 month post ARV initiation, 3.3% at 4 months, 6.1% at 12 months and 2.8% at 24 months while the prevalence were 10.5%,11.5%, 20.4% and 16.7% respectively. Older age and male gender were independently associated with prevalence of renal impairment.

Conclusion: Renal dysfunction in patients initiated on TDF based regimen in this study varied and were relatively small when compared to the prevalence of renal dysfunction at initiation. Majority of the decline in CrCl were transient and patients were found to have recovered after further follow up. It is recommended that the frequency of renal function monitoring in patients on TDF regimen be done within programmatic guidelines based on patients' risk factors and potential poor outcomes.

Keywords: Tenofovir, HIV/AIDS, antiretroviral therapy, nephrotoxicity, South Africa.

DEDICATION

Dedicated to my wife and children for their support and understanding.

ACKNOWLEDGEMENT

I owe a debt of gratitude to my supervisors Prof Derek Hellenberg and Dr Tasleem Ras for their guidance throughout my registrar programme. Special thanks to Michells Plain CHC particularly Dr Neal David, staff of ARV Clinc and its Record Department for allowing me to conduct this study in their facility. Profound gratitude to my wife and children for their support. Big thanks to colleagues and friends for their contributions.

TABLES AND FIGURES

ABBREVIATIONS

ARV	Antiretroviral or antiretrovirus
ART	Antiretroviral therapy
AIDS	Acquired immunodeficiency syndrome
BMI	Body mass index
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
CD4	Cluster of differentiation 4
CG	Cockcroft-Gault
CHC	Community health centre
CrCl	Creatinine clearance
EFV	Efavirenz
eGFR	Estimated glomerular filtration rates
FHS	Faculty of Health Sciences
FDC	Fixed dose combination
FTC	Emtricitabine
HAART	Highly active antiretroviral therapy
Hb	Haemoblobin
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
LTFU	Lost to follow up
MOU	Midwife obstetric unit
PMTCT	Prevention of maternal to child transmission
PI	Protease inhibitor
PI/r	Retonavir boosted rotease inhibitor

SD	Standard deviation
Sqm	Square metre
TDF	Tenofovir orTenofovir disoproxil fumarate
UCT	University of Cape Town
VL	Viral load
WHO	World Health Organisation

CHAPTER ONE: INTRODUCTION AND LITERATURE REVIEW

Tenofovir disoproxil fumarate (TDF) based combination is the preferred first line therapy according to the World Health Organisation (WHO) 2016 antiretroviral therapy (ART) guidelines.[1] TDF is extensively used globally and is now the most prescribed antiretroviral (ARV) drug.[1] Its high antiviral activity, favourable metabolic profile and availability in fixed dose combination (FDC), which improves adherence, are responsible for its success.[1] However, TDF has been found to cause renal impairment, and several studies have shown TDF-related renal dysfunction.[2] In addition to ARV related nephropathy, the range of human immunodeficiency virus (HIV)-related nephropathy includes HIV-associated nephropathy (HIVAN), HIV-immune complex kidney disease, and those due to co-morbidities such as diabetes mellitus and hypertension.[3] The risk of acute and chronic renal dysfunction is more significant in HIV patients than in the general population, and renal disease in HIV patients is associated with poor outcomes, with higher mortality.[4]

Studies have shown multiple risk factors for renal dysfunction in HIV patients.[5-10] Kefeni *et al.*[5] study in Ethiopia, using chronic kidney disease epidemiology collaboration (CKD-EPI) equation to estimate the glomerular filtration rate (GFR) showed that high prevalence of renal dysfunction in HIV patients was associated with hypertension, diabetes, cigarette smoking, and low CD4 count.[5] Furthermore, Calza *et al.*[10] in Italy using the same estimated GFR (eGFR) equation found male gender, age greater than 50years, elevated triglyceride, CD4 count less than 200, hypertension, diabetes mellitus and TDF use particularly in combination with protease inhibitors (PI) as the risk factors for renal dysfunction in HIV patients.[10] Additional renal dysfunction risk factors are body mass index (BMI) less than 18.8kg/sqm and viral loads (VL) above 1000 cp/ml according to Ekat *et al.*[9] and Mwemezi *et al.*[7] respectively.

Several studies have shown increased prevalence of renal dysfunction in HIV patients prior to initiation of ARV[11] and while they are on ARV.[5-8] Also, the method of estimating GFR may have a major influence on the prevalence of renal dysfunction, as shown by studies with outcomes based on more than one GFR methods.[3] Furthermore, TDF induced nephrotoxicity has been reported worldwide using various methods of assessing and defining renal impairment such as eGFR and creatinine level.[2, 11-14] The risk factors for TDF induced nephrotoxicity include smaller body weight and BMI, old age, low CD4 count, high HIV VL, concurrent nephrotoxic drugs, hepatitis C infection, current cigarette smoking, the length of time on the ART, combination with PI, hypertension, diabetes mellitus, and baseline proteinuria.[12, 13, 15-17]

The prevalence and incidence of TDF induced nephrotoxicity vary depending on the method used and length of the study.[2, 11-14] Biomarkers frequently used to assess and monitor renal function include serum creatinine, for estimating GFR, and the presence of proteinuria. However, these biomarkers have many shortcomings.[18] GFR estimates are not absolutely verified in HIV patients.[4, 19] The CKD-EPI equation seems to give the best approximations in those stable on ART, and creatinine clearance(CrCl) using Cockcroft-Gault (CG) equation remains the recommended method for drug dosing.[4] However, there are pros and cons for all methods of estimating GFR1.[4, 19-21] Also many drugs including ARV can affect creatinine secretion without affecting GFR.[4] Moreover, high animal protein diets and supplements containing creatine can elevate serum creatinine level causing invalid estimation of GFR.[4]

A Nishijima *et al.*[12] study in Japan showed that TDF-related renal dysfunction occurred in 19.6% patients (incidence:10.5 per 100 person-years) with univariate analysis showing that the incidence of the renal dysfunction was significantly associated with smaller body weight and BMI. High baseline eGFR, low serum creatinine, old age, low CD4 count, high HIV VL, concurrent nephrotoxic drugs, hepatitis C infection, and current cigarette smoking were also found to be associated with TDF -related renal dysfunction.[12] The Nishijima *et al.* study used Modification of Diet in Renal Disease (MDRD) to estimate GFR and defined TDF-associated renal

dysfunction as greater than 25% decrease in eGFR relative to the baseline.[12] Similarly, Lee *et al.*[22] in their study in Korea, using the same definition but with CKD-EPI equation, reported incidence of TDF renal dysfunction as 9.66 per 100 person-years and discovered that advanced stage of HIV infection was a significant risk factor for TDF induced renal dysfunction.[22]

A multicentre Cao *et al.*[23] study in China compared renal dysfunction in patients on second line ART regimen containing TDF and ritonavir boosted protease inhibitor (PI/r) with ART naïve patients initiated on non TDF based combination, using MDRD for eGFR, found that a TDF and PI/r ART regimen resulted in more renal dysfunction.[23] On the other hand, a single centre study by Tan *et al.*[24] in China using CKD-EPI formula to estimate GFR and defining TDF related renal dysfunction as reduction in eGFR >25% from baseline or eGFR < 90ml/min/1.73sqm reported low cumulative incidence (2.7%) of TDF related renal dysfunction in young ART naïve patients with no comorbidities. The associated risk factors in their study were lower body weight and longer duration of exposure to TDF.[24]

Pujari *et al.*[25] in their retrospective comparative study between a low socioeconomic community in India and a developed community in United Kingdom, using MDRD to estimate GFR, discovered that TDF nephrotoxicity is more likely to occur in a low socioeconomic community, with associated risk factors including hypertension, diabetes mellitus and concomitant use of nephrotoxic drugs.[25] Another study in India by Kumarasamy *et al.,*[15] using CG equation to calculate CrCl to estimate GFR showed high prevalence of TDF related renal dysfunction, with risk factors including increased age, low BMI, low baseline CD4 count, hypertension and diabetes mellitus but excluding PI.[15] They concluded that the prevalence in their study was higher than in other well developed settings and suggested that renal function should be monitored in resource restricted settings.[15]

Quesada *et al.*[17] study in Spain, which used MDRD equation to estimate GFR, showed high incidence of moderate renal dysfunction (eGFR< 60ml/min) due to TDF, while severe (eGFR<30ml/min) TDF related renal

dysfunction was rare.[17] Risk factors for TDF renal dysfunction in their study include age, duration of treatment with TDF, elevated baseline creatinine levels, and treatment with PI/r combinations.[17]

Scherzer *et al.*[26] which used MDRD equation to calculate eGFR in their study of US veterans stated that “In Cox proportional hazards models that adjusted for age, gender, and race, each year of cumulative exposure to tenofovir was associated with a 30% increase in the risk of proteinuria. Tenofovir use was also associated with an 11% increased risk of rapid decline per year of exposure, and a 33% increased risk of chronic kidney disease (CKD) per year of exposure in fully adjusted time-dependent Cox models”.[26]

Agbaji *et al.*[27] study in Nigeria in which they defined renal dysfunction as eGFR <60 ml/min/1.73sqm (using MDRD equation) or 2-fold increase in serum creatinine (SCr) above baseline or a 50% decline in CrCl (calculated using the CG equation) from baseline on 1 or more measurements, showed that long-term exposure to TDF-based ART greatly increase the odds of renal dysfunction.[27] Similarly, Debeb *et al.*[28] showed high incidence of renal dysfunction in TDF users in their study in Ethiopia in which they defined renal dysfunction as eGFR<60ml/min/1.73sqm but used CKD-EPI equation to estimate GFR. The risk factors in their study include age ≥55years, diabetes mellitus, concurrent use of nephrotoxic drug, and combination with PI/r.[28] Conversely, Nyende *et al.*[29] study in Uganda, using the same method to estimate GFR but defining TDF related renal dysfunction as either eGRF <60ml/min/1.73sqm or proteinuria of ≥2+ with glycosuria but normal blood sugar, showed low prevalence(2.52%) of TDF related renal dysfunction.[29]

Moreover, Wantakisha *et al.*[30] study in Zambia, which defined renal dysfunction as CrCl <50ml/min calculated using the CG equation to estimate GFR, showed high point prevalence (18.6%) of renal dysfunction in patients using TDF at 18 months follow up with old age and low CD4 count as the major risk factors.[30] In contrast, Bygrave *et al.*[31] study in Lesotho, using the same CG equation to calculate CrCl and defining renal dysfunction as CrCl <90ml/min, reported that TDF associated renal dysfunction was rare and

mild.[31] Similar studies from South Africa, Brennan *et al.*[2] and Kamkuemah *et al.*[14] , also using CG equation to calculate CrCl, reported low prevalence of TDF associated renal dysfunction. Brennan *et al.*[2] study showed that 2.4% of patients experienced nephrotoxicity, while Kamkuemah *et al.*[14] study in a community health centre (CHC) in Cape Town, found that 3% of patients initiated on TDF based ART developed renal impairment.

There is a scarcity of studies in Sub-Saharan Africa on TDF associated nephrotoxicity despite the fact that this region accounts for the largest number of people living with HIV/ Acquired immunodeficiency syndrome (AIDS) and ART usage.[2, 14] Furthermore, only a few studies were conducted in South Africa on TDF related nephrotoxicity despite the fact that South Africa has the largest ART roll out in the world with a TDF based regimen as the first line treatment.[2, 14] There is little knowledge regarding the effect of renal impairment on treatment outcomes in patients initiated on TDF in resource-limited settings.[2] Some studies show low rates of TDF associated renal failure and nephrotoxicity, while others suggest a higher risk amongst patients with renal impairment at initiation of TDF compared to those with normal renal function.[2]

Therefore, in order to design meaningful TDF-based ART regimen and monitoring strategies, it is very important to identify the prevalence and incidence of TDF associated nephrotoxicity for each population and geographical location, and to understand the reasons for the observed differences vis-a-vis the risk factors and pattern. At present, there are no data available on the TDF associated nephrotoxicity in Mitchells Plain, Cape Town, South Africa. This study was conducted in the Mitchells Plain ARV Clinic in an attempt to understand the TDF associated nephrotoxicity in this local population. It is envisaged that knowledge of the prevalence and incidence of TDF associated nephrotoxicity in this ARV Clinic with the pattern of occurrence and associated risk factors, would assist in making rational recommendations regarding treatment and monitoring of patients in this community.

PURPOSE OF THE STUDY

AIM

To look at incidence/prevalence of renal dysfunction and associations with TDF use in the population attending the Mitchells Plain ARV Clinic in Cape Town, South Africa.

OBJECTIVES

1. To document renal dysfunction in patient initiated on TDF
2. To describe the pattern of renal dysfunction occurrence in TDF
3. To determine asssociated factors involved
4. To make recommendations regarding TDF prescription and monitoring of patients on TDF based ART

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CHAPTER TWO: PUBLICATION-READY MANUSCRIPT

ABSTRACT

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INTRODUCTION

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A multicentre Cao *et al.*[23] study in China compared renal dysfunction in patients on second line ART regimen containing TDF and ritonavir boosted protease inhibitor(PI/r) with ART naïve patients initiated on non TDF based combination, using MDRD for eGFR, found that a TDF and PI/r ART regimen resulted in more renal dysfunction.[23] On the other hand, a single centre study by Tan *et al.*[24] in China using CKD-EPI formula to estimate GFR and defining TDF related renal dysfunction as reduction in eGFR >25% from baseline or eGFR < 90ml/min/1.73sqm reported low cumulative incidence (2.7%) of TDF related renal dysfunction in young ART naïve patients with no comorbidities. The associated risk factors in their study were lower body weight and longer duration of exposure to TDF.[24]

Pujari *et al.*[25] in their retrospective comparative study between a low socioeconomic community in India and a developed community in United Kingdom, using MDRD to estimate GFR, discovered that TDF nephrotoxicity is more likely to occur in a low socioeconomic community, with associated risk factors including hypertension, diabetes mellitus and concomitant use of nephrotoxic drugs.[25] Another study in India by Kumarasamy *et al.,*[15] using CG equation to calculate CrCl to estimate GFR, showed high prevalence of TDF related renal dysfunction, with risk factors including increased age, low BMI, low baseline CD4 count, hypertension and diabetes mellitus but excluding PI.[15] They concluded that the prevalence in their study was higher than in other well developed settings and suggested that renal function should be monitored in resource restricted settings.[15]

Quesada *et al.*[17] study in Spain, which used MDRD equation to estimate GFR, showed high incidence of moderate renal dysfunction (eGFR< 60ml/min) due to TDF, while severe (eGFR<30ml/min) TDF related renal dysfunction was rare.[17] Risk factors for TDF renal dysfunction in their study include age, duration of treatment with TDF, elevated baseline creatinine levels, and treatment with PI/r combinations.[17]

Scherzer *et al.*[26] which used MDRD equation to calculate eGFR in their study of US veterans stated that “In Cox proportional hazards models that adjusted for age, gender, and race, each year of cumulative exposure to tenofovir was associated with a 30% increase in the risk of proteinuria. Tenofovir use was also associated with an 11% increased risk of rapid decline per year of exposure, and a 33% increased risk of chronic kidney disease (CKD) per year of exposure in fully adjusted time-dependent Cox models”.[26]

Agbaji *et al.*[27] study in Nigeria in which they defined renal dysfunction as eGFR <60 ml/min/1.73sqm (using MDRD equation) or 2-fold increase in serum creatinine (SCr) above baseline or a 50% decline in CrCl (calculated using the CG equation) from baseline on 1 or more measurements, showed that long-term exposure to TDF-based ART greatly increase the odds of renal dysfunction.[27] Similarly, Debeb *et al.*[28] showed high incidence of renal dysfunction in TDF users in their study in Ethiopia in which they defined renal dysfunction as eGFR<60ml/min/1.73sqm but used CKD-EPI equation to estimate GFR. The risk factors in their study include age ≥55years, diabetes mellitus, concurrent use of nephrotoxic drug, and combination with PI/r.[28] Conversely, Nyende *et al.*[29] study in Uganda, using the same method to estimate GFR but defining TDF related renal dysfunction as either eGRF <60ml/min/1.73sqm or proteinuria of ≥2+ with glycosuria but normal blood sugar, showed low prevalence (2.52%) of TDF related renal dysfunction.[29]

Moreover, Wantakisha *et al.*[30] study in Zambia, which defined renal dysfunction as CrCl <50ml/min calculated using the CG equation to estimate GFR, showed high point prevalence (18.6%) of renal dysfunction in patients using TDF at 18 months follow up with old age and low CD4 count as the major risk factors.[30] In contrast, Bygrave *et al.*[31] study in Lesotho, using the same CG equation to calculate CrCl and defining renal dysfunction as CrCl <90ml/min, reported that TDF associated renal dysfunction was rare and mild.[31] Similar studies from South Africa, Brennan *et al.*[2] and Kamkuemah *et al.*[14], also using CG equation to calculate CrCl, reported low prevalence of TDF associated renal dysfunction. Brennan *et al.*[2] study showed that 2.4% of patients experienced nephrotoxicity, while Kamkuemah *et al.*[14] study in a

community health centre (CHC) in Cape Town, found that 3% of patients initiated on TDF based ART developed renal impairment.

There is a scarcity of studies in Sub-Saharan Africa on TDF associated nephrotoxicity despite the fact that this region accounts for the largest number of people living with HIV/ Acquired immunodeficiency syndrome (AIDS) and ART usage.[2, 14] Furthermore, only a few studies were conducted in South Africa on TDF related nephrotoxicity despite the fact that South Africa has the largest ART roll out in the world with a TDF based regimen as the first line treatment.[2, 14] There is little knowledge regarding the effect of renal impairment on treatment outcomes in patients initiated on TDF in resource-limited settings.[2] Some studies show low rates of TDF associated renal failure and nephrotoxicity, while others suggest a higher risk amongst patients with renal impairment at initiation of TDF compared to those with normal renal function.[2]

Therefore, in order to design meaningful TDF-based ART regimen and monitoring strategies, it is very important to identify the prevalence and incidence of TDF associated nephrotoxicity for each population and geographical location, and to understand the reasons for the observed differences vis-a-vis the risk factors and pattern. At present, there are no data available on the TDF associated nephrotoxicity in Mitchells Plain, Cape Town, South Africa. This study was conducted in the Mitchells Plain ARV Clinic in an attempt to understand the TDF associated nephrotoxicity in this local population. It is envisaged that knowledge of the prevalence and incidence of TDF associated nephrotoxicity in this ARV Clinic with the pattern of occurrence and associated risk factors, would assist in making rational recommendations regarding treatment and monitoring of patients in this community.

METHODOLOGY

STUDY DESIGN

The study was conducted by reviewing retrospective records from the Mitchell's Plain CHC ARV Clinic of all ART naïve HIV positive adults initiated on a TDF based ART regimen in between January 2016 to June 2016. The follow up parameters in the patients' medical records were reviewed from February 2016 to June 2018 for renal dysfunction associated with TDF.

To determine renal dysfunction, change in renal function of the patients (who met the inclusion criteria) was extracted from the medical records based on ART guidelines over the 2-year study period. The creatinine clearance(CrCl), calculated using the Cockcroft–Gault equation was used because it is the recommended method for drug dosing.[4] CrCl was deemed to be appropriate for this study because similar studies in Southern Africa used it.[14, 30, 31] Renal function was categorised into normal, mild, moderate and severe reduction in renal function based on values >90, 60–89, 30–59 and <30 ml/min respectively. Incident renal function reduction was defined as any absolute decrease in CrCl >10 ml/min from baseline value.[14]

STUDY POPULATION

Adult patients attending the ARV Clinic at Mitchell's Plain CHC in Mitchell's Plain, Cape Town, Western Cape Province, South Africa.

Inclusion criteria

- Patient's age ≥ 18years
- ARV naïve initiated on TDF based regimen
- No contraindication to TDF
- Renal function at initiation:
    - eGFR > 50
    - CrCl>50

- No medical co-morbidities that affect renal function such as hypertension and diabetes at initiation of ARV
- Not on nephrotoxic drugs at initiation
- Non-pregnant women

Exclusion criteria

- Patients aged < 18years
- ARV experienced patients
- Contraindication to TDF
- Patients with renal function:
    - eGFR≤ 50
    - CrCl ≤50
- Patients with co-morbidities that affect renal function such as hypertension diabetes at initiation of ARV
- Patients on nephrotoxic drugs at initiation
- Pregnant women

SAMPLING METHOD

Accessible medical records of patients between January 2016 and June 2016 who met the inclusion criteria at Mitchell's Plain CHC ARV Clinic in Mitchell's Plain, Cape Town were selected and reviewed.

SAMPLE SIZE

The sample size(*N*) of 210 folders needed to be reviewed as was calculated based on a review of similar studies, to achieve a power of 0.90 for multiple linear regression, given a medium effect size (Cohen's f^2=0.15), 10 predictor

variables and an alpha of 0.005 (a more conservative alpha value corrected for running multiple comparisons).

However, due to various reasons and limitations, only 87 out of 411 patients who were started on ARV in the Mitchell's Plain CHC met the inclusion criteria.

DATA COLLECTION METHODS

A checklist was used as a data collection tool (Appendix 1).

The checklist contained the following information from medical records:

- Demographic data
- Baseline at initiation of ART: WHO stage, CD_4 count, Creatinine, Haemoblobin(Hb), body mass index (BMI), medical/surgical history, drugs,
- ART regimen
- Renal function indicators: Creatinine level, eGFR and CrCl

DATA ANALYSIS

The data of the 87 patients were sent to a statistician for analysis. The analysis was based on a review of similar studies. Initial analysis was the determination of renal function at baseline and follow up to estimate the incidence and prevalence of nephrotoxicity. A linear regression was run to determine significant predictors of mean change in CrCl during the first 24 months on ART. Logistic regression models were run to determine significant predictors for the development of nephrotoxicity across the two-year period from ART initiation.

ETHICS

Privacy and confidentiality were respected when handling the medical records by:

- not using any personally identifiable information such as names, identity numbers or addresses
- de-identification, done by allocating numbers to patients' medical records that were different from their folder numbers without their names. This will make the folders traceable for research audit.

Ethical approval was obtained from The Ethics Review Committee of the Department of Health, Western Cape Government, the University of Cape Town (UCT) Faculty of Health Sciences (FHS) Human Research Ethics Committee (HREC), reference number 705/2017, and the study site. The study also complied with the latest version of the Declaration of Helsinki (2008).

RESULTS

Four hundred and eleven patients were started on ARV during the period under review (January 2016 to June 2016). A total of 324 were excluded due to various reasons such as folders not found (45), patients belonged to midwife obstetrics unit (MOU)/prevention of maternal to child transmission (PMTCT) programme (146), Transferred in (89), less than 18years of age (18), comorbidity/Not on TDF (26).

The baseline characteristics of 87 patients included in the analysis are shown in Table 1. 56%(n=49) of the sample were female and 97%(n=84) were on tenofovir (TDF), emtricitabine (FTC) and efavirenz (EFV) fixed dose combination (FDC) as their ARV treatment. Mean age of 34 years (SD 8.95 years). Most patients, (83%), had normal renal function(CrCl>90ml/min) at initiation of ARV, 15% had mildly reduced CrCl, and 1% patient had moderately reduced CrCl. Less than a quarter of the cohort had advanced immunosuppression at baseline. 16 patients (18%) had WHO Stage III and 4 patients (5%) had Stage IV disease). Mean CD4 cell count of 285.08 cell/mm3 (SD = 190.84).

In a multivariable logistic regression model, older age [OR = 1.11; 95% CI (1.03–1.19), *p* =0.005], was associated with an increased probability of non-normal (i.e., mild or moderate) renal function at baseline.

Table 1. Baseline demographic, clinical and laboratory characteristics

	Normal *N* = 72	Mild Impairment *N* = 13	Moderate Impairment *N* = 1	Total *N* = 87*
Mean Age (years)	32.72	41.15	36	34.08
Age group, %				
<29 years	21(29.2%)	1(7.7%)	-	22

29-34 years	21(29.2%)	2(15.4%)	-	23
35-41 years	20(27.8%)	4(30.8%)	1(100%)	26*
>41 years	10(13.9%)	6(46.2%)	-	16
Sex, %				
Male	27(37.5%)	10(76.9%)		38(43.7%)*
Female	45(62.5%)	3(23.1%)	1(100%)	49(56.3%)
WHO disease stage, %				
I	34(47.2%)	3(25%)	-	37
II	23(31.9%)	5(41.7%)	-	29
III	12(16.7%)	4(33.3%)	-	16
IV	3(4.2%)	0	1(100%)	4
CD4 category, %				
<100	13(18.1%)	3(23.1%)	1(100%)	17
100-200	9(12.5%)	1(7.7%)	-	11
>200	50(69.4%)	9(69.3%)	-	59

*one male patient in the age group 35-41 years had no baseline CrCl because weight was not recorded.

The baseline and follow-up of parameters are as shown in Table 2. CrCl values were available for 86 patients at baseline, 67, 61 and 49 patients at month-1, -4 and -12 respectively. At month-24, only 40 patients medical records could be traced, and CrCl measures were available for 36 because

weight of 4 patients were not on record. By the end of the second year 47 patients had been lost to follow up for various reasons (overall retention, 46%).

Table 2. Change in clinical and laboratory characteristics

	N	Minimum	Maximum	Mean	SD
Baseline					
Age	87	18	57	34.08	8.95
Weight	86*	39	102	63.85	14.40
CD4	87	5	1183	285.08	190.84
Creatinine	87	33	103	65.13	13.81
eGFR	87	64.5	229.7	115.6	25.43
CrCl	86*	47	204	119.64	30.21
1-month					
Weight	67	41.3	99.6	66.41	14.49
Creatinine	70	38	91	63.74	12.55
eGFR	70	67.4	191.8	116.96	24.65
CrCl	67	69	201	124.33	30.12
4-months					
Weight	61	41.3	102.6	67.26	13.99
Creatinine	62	26	137	64.44	16.2

eGFR	62	52	249.3	117.52	28.34
CrCl	61	53	197	128.16	32.37
12-months					
Weight	49	44.3	106.3	70.42	15.94
Creatinine	51	43	118	66.49	13.46
eGFR	51	57	153.2	107.86	18.67
CrCl	49	69	198	124.84	33.53
24-months					
Weight	36	36	107	73.11	16.87
Creatinine	40	43	549	80.1	84.63
eGFR	40	9	157.8	103.29	25.76
CrCl	36	8	208	127.17	41.1

⁎one male patient in the age group 35-41 years had no baseline CrCl because weight was not recorded.

Figures 1, 2, 3, and 4 display CrCl profiles by patient demographic and disease characteristics.

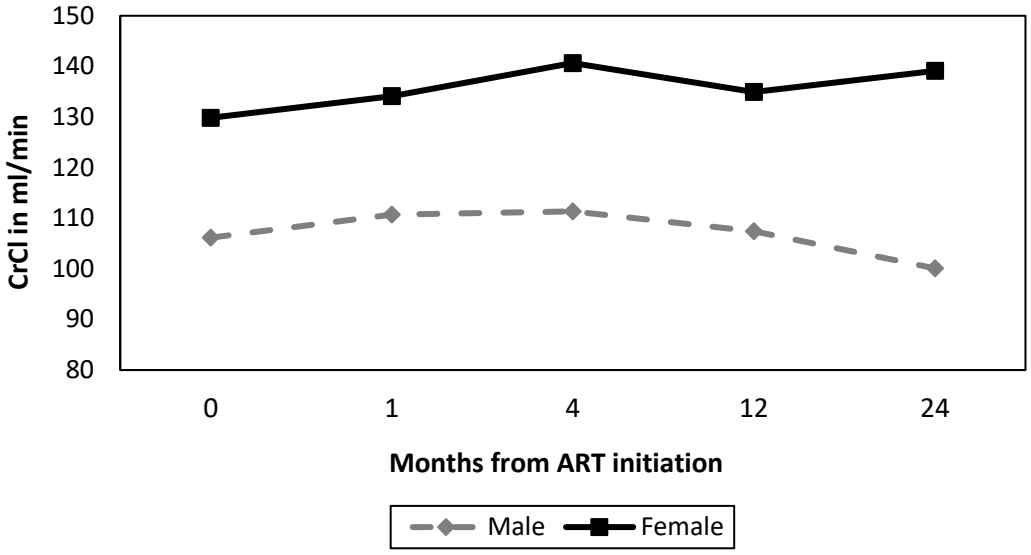

Figure 1 Profile plot by gender

Figure 1 shows notable CrCl profile differences exist between gender. Women had higher average CrCl than men at all time points (all *p*'s < 0.007).

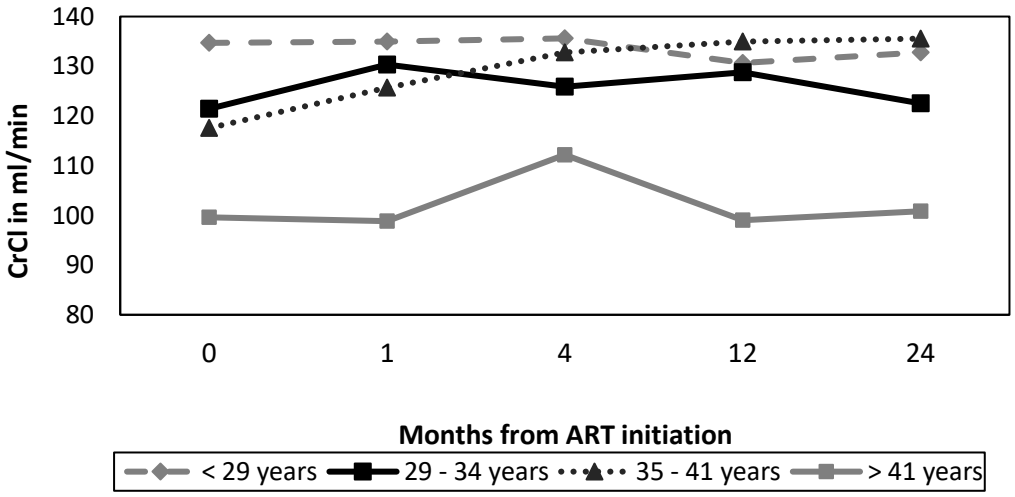

Figure 2 Profile plot by age

Figure 2 shows presence of significant difference in age group ClCr. On average, the oldest age group (age >41 years) had a lower average CrCl

than the other age groups. At baseline and one-month, the oldest age group had significantly lower CrCl compared to the youngest age group (age < 29 years) (p =0.002 and 0.008 respectively), at one-month they also had significantly lower CrCl compared to patients who were 35-41 years of age (p = 0.024), and at 12 -months had significantly lower CrCl compared to patients who were 29-34 years of age (p = 0.022).

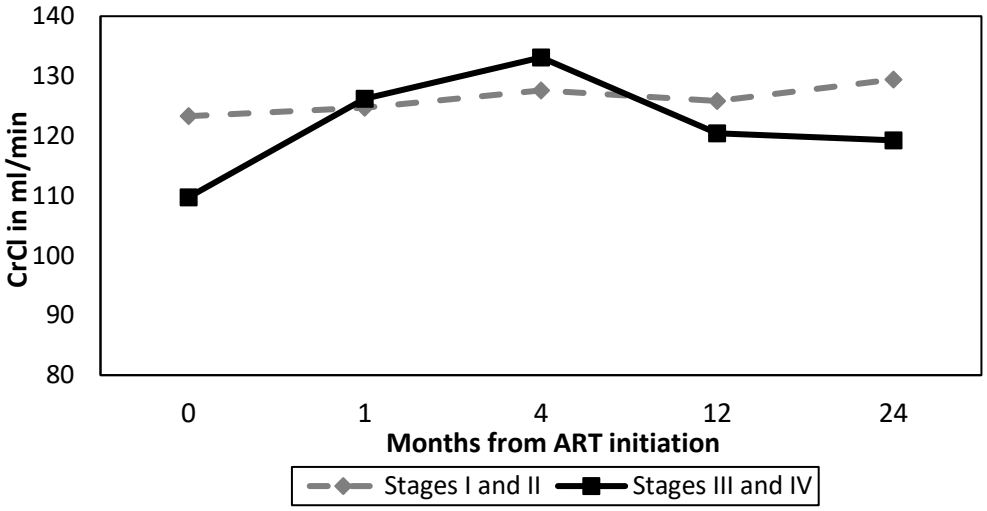

Figure 3 Profile plot by WHO disease stage

Figure 3 shows that there were no significant differences in average CrCl profiles by baseline WHO stage categories (p = 0.078).

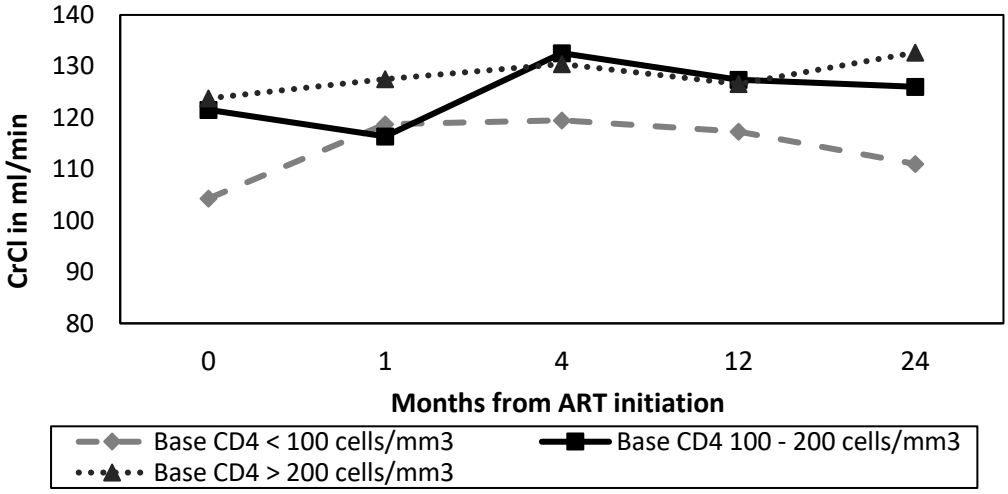

Figure 4 Profile plot by baseline CD4 cell count

Figure 4 shows that there were no significant differences in average CrCl profiles by baseline CD4 count (p = 0.062).

A linear regression analysis found that baseline, one-month and four-month CrCl levels were the only significant predictors of CrCl trajectories from baseline to 12-months post-ARV initiation. CrCl levels decreased by 0.75 ml/min for every one-unit increase in baseline CrCl (p < 0.001, 95% CI: -0.97 – (-0.52)), increased by 0.38 ml/min for every one-unit increase in one-month CrCl levels (p = 0.005, 95% CI: 0.12 – 0.63), and increased by 0.34 ml/min for every one-unit increase in four-month CrCl levels (p = 0.017, 95% CI: 0.07 – 0.62).

On the other hand, WHO stage and baseline CrCl levels were significant predictors of CrCl trajectories from baseline to 4-months post-ARV initiation. Patients with Stages III and IV disease experienced a 14.3 ml/min higher increase in CrCl levels compared to patients with Stages I and II disease (p = 0.028, 95% CI: 1.63 – 26.99). The decrease in CrCl levels by 0.34 ml/min for every one-unit increase in baseline CrCl (p = 0.004, 95% CI: -0.12 – 0.44) is statistically insignificant. There were no predictors of CrCl trajectories from baseline to 24-months.

Logistic regression analyses found a positive association between baseline CrCl levels and developing nephrotoxicity at 1-month post-ARV initiation. For every one-unit increase in baseline CrCl, the odds of developing nephrotoxicity increased by a factor of 1.04 (95% CI: 1.02 – 1.07, p = 0.002). No other significant associations were found.

DISCUSSION

The result of this study shows that the incidence of TDF related renal dysfunction varied and were relatively small when compared to the prevalence of renal impairment at initiation of TDF based ARV regimen. This is on par with the results of similar studies done in Lesotho and South Africa that also used CrCl calculated using CG equation.[2, 14, 31] Bygrave *et al.*[31] study in Lesotho showed that TDF associated renal dysfunction was rare and mild while Brennan *et al*.[2] and Kamkuemah *et al.*[14] studies in South Africa reported low prevalence of 2.4% and 3% respectively. However, this result is in contrast to Wantakisha et al.[30] study in Zambia which showed high point prevalence of 18.6% of TDF associated renal dysfunction despite using CG equation to calculate CrCl. Exclusion of patients with comorbidities that can cause renal dysfunction from this study, lower mean age of < 40years, more than 80% of patient having normal baseline renal function, mean baseline CD4 count > 250 and less than 25% of patients having advanced HIV may be the reason for the low incidence of TDF associated renal dysfunction in this study.[15-17]

At initiation, about 16% (15% mild and 1% moderate) had renal impairment. It is not uncommon to find renal dysfunction at ARV initiation because HIV, on its own, is a nephrotoxic virus.[2, 11, 24, 32] HIV-related nephropathy includes HIV-associated nephropathy (HIVAN), HIV-immune complex kidney disease, and those due to co-morbidities such as diabetes mellitus and hypertension.[3] Bygrave *et al.*[31] and Fritzsche *et al.*[32] noted in their studies that the baseline renal function reported among patients initiating ARV in Africa is variable.This study baseline renal dysfunction prevalence is, however, lower than similar studies in South Africa and other Sub Saharan nations: 21% in Gugulethu, South Africa,[14] 35.7% in Johannesburg, South Africa,[2] 45% in Senegal[33] and 63.1% in Tanzania.[11] The prevalence of renal dysfunction in HIV patients differs significantly between studies, depending on region, population studied, study design, and methodology used to define renal dysfunction.[3, 10] The low prevalence of renal dysfunction at initiation of ARV in this study may be related to the exclusion of co-morbidities that cause renal impairment.

This study showed that older age was associated with an increased probability of non-normal (i.e., mild or moderate dysfunction) renal function at baseline. This is similar to other studies, but, in contrast, was limited by the available number of baseline variables used for data analysis in other studies; such as haemoglobin (Hb) and body mass index (BMI) which were linked with baseline renal dysfunction, in addition to older age.[2, 12, 14, 31, 33, 34] This association is expected because studies have shown that renal function decreases with age due to ageing process in the kidney and contribution from age related co-morbidities.[35, 36] Usage of CG equation to estimate GFR can also be contributory to higher renal dysfunction with increased age because muscle mass decreases with age which lead to over estimation of renal dysfunction by CG equation.[37-40]

The incidence of CrCl < 90ml/min were 1.5% at 1 month post ARV initiation, 3.3% at 4 months, 6.1% at 12 months and 2.8% at 24 months while the prevalence were 10.5%, 11.5%, 20.4% and 16.7% respectively. Both incidence and prevalence were highest at 12-month. The reason for this trend could be related to the significantly reduced sample size at 24 months due to loss to follow up (LTFU), however, studies have shown variable incidence/prevalence in TDF associated renal dysfunction during the course of the studies.[13, 16] Majority of the decline in CrCl in this study were transient and patients were found to have recovered after further follow up which is comparable to Kamkuemah *et al.*[14] study where overall renal function improved in most of the patients started on TDF regimen during their study. This finding is also similar to Bygrave *et al.*[31] observation in their cohort, in which greater number of patients who developed a CrCl <50 ml/min dropped by less than 10 ml/min and subsequently returned above the threshold. Mulenga *et al.*[41] study demonstrated improvement in renal function of patients with renal dysfunction upon starting ARV even with regimen containing TDF because ARV generally improves HIVAN.[41]

Incident renal function decrease of more than 10ml/min from baseline was most common in the first month after the initiation of ARV treament which is

in contrast to similar study by Kamkuemah *et al.*[14] in South Africa which showed greatest incidence in the first 4 months on ARV for incident renal function decrease of more than 10ml/min from baseline. However, it is in accordance with the finding of Yazie *et al.*[16] study in Ethiopia which showed more decrease in renal function in the first month on ARV but defined it as eGFR>25% from baseline. Only one patient, at 24-month, had CrCl decline below 50ml/min over the entire 24 month period of this study which is similar to study done by Kamkuemah *et al.*[14] which reported few patients over 12month period.

Moreover, the impairment in renal function was found to be associated with male gender and older age group at initiation of ART in this study. Prepondrance of male susceptibility to TDF associated renal dysfunction in this study is similar to the findings of Pinto Neto *et al.*[42] and Calza *et al.*[10] studies. This study concur with several studies which documented patients older than 50years as risk factor for TDF associated renal impairment.[10, 14, 16, 30, 42-45] Older age is a classic risk factor for renal dysfunction due to age related deterioration in renal function, co-morbidities and use of CG equation to estimate GFR.[35-40] In the great proportion of patients, there was improvement in renal function after commencing TDF-based ARV regimen during this study. These findings are similar to previous studies done in South Africa and other parts of the world.[14, 24]

The baseline, 1-month and 4-month CrCl levels were the only significant predictors of CrCl trajectories from baseline to 12-months post-ARV initiation. On the other hand, WHO stage and baseline CrCl levels were significant predictors of CrCl trajectories from baseline to 4-months post-ART initiation. However, this study did not show any predictor of CrCl trajectories from baseline to 24-months. These findings contrast with previous studies in South Africa where serum creatinine testing after 4 months on ART was more predictive of renal function after 12 months than earlier tests at 1 and 2 months on treatment.[2, 14] The reason for the difference may be related to the study population because Kamkuemah *et al.*[14] noted that patients with renal

dysfunction at month 1 had other comorbidities. This study findings justify the checking of the serum creatinine at month 1 and month 4 after initiation of TDF based ART regimen in the study setting.

This study analysis shows risk factors for prevalent renal function decline in patients initiating ARV that are similar to those documented by previous studies from sub-Saharan Africa such as older age.[14, 16, 30, 34] This may be due to the fact that older age is known to be a notable predictor of chronic renal dysfunction in the wider society.[34] Moreover, using CG equation to estimate GFR can also contribute to higher renal dysfunction in older age because muscle mass decreases with age which lead to over estimation of renal dysfunction by CG equation.[37-40] Furthermore, this study also shows that males had higher relative odds of renal impairment at baseline and throughout the 2-year period which is in support of Pinto Neto *et al.*[42] study in Brazil and Calza *et al.*[10] study in Italy but in contrast to similar study done by Kamkuemah *et al.*[14] in South Africa which reported higher relative odds of renal dysfunction in women at baseline. Studies have shown variances in gender prevalence of CKD due to gender specific disparity in anatomy of the kidney and impact of sex hormones.[46] A systematic review and meta-analysis on global prevalence of CKD by Hill *et al.*[47] reported studies showing contrasting gender prevalence of CKD depending on the region, study population, study design and methodology.[47]

Incidental findings in this study include substantial number of patients lost to follow up (LTFU) due to various reasons and missing data in patients' medical records. Several similar studies encountered missing data which inadvertently limited covariates available for analysis.[31, 43] Out of the 87 patients that met the criteria for the study at baseline, 47 of them were LTFU by month 24 giving overall retention of 46%. Many studies have reported that LTFU poses significant challenges to the successful execution of ART programmes.[48-51] Kaplan *et al.*[49] in their systematic review and meta-analysis of published studies in South Africa cited that "a review from 2007 of ART programmes in sub-Saharan Africa estimated 20% attrition at 6 months

and between 25% and 75% at 2 years depending on the estimation method used”.[49]

STUDY LIMITATIONS

The study had several limitations besides being retrospective design which made it prone to confounders and inability to compare the significance of baseline characteristics of patients LTFU with those retained for analysis.

Firstly, the folders selected for the study were the ones that the record department could retrieve from their archive and did not include all the patients who started ARV during the study period. Over 300 patients were excluded from the study due to various reasons such as missing data, folders not found, transfer to another facility. This could have introduced selection bias. Secondly, a small sample size of 87, far below the 210 participants calculated to adequately power the study, could have resulted in a lack of precision for the outcome in this study.

Thirdly, only 46% of the patients were retained at the end of the study period. Many patients were lost to follow up due to various reasons at different points in the study. This, in addition to missing data, limited the number of covariates for data analysis. Moreover, data on concurrent self-medication with over-the counter, traditional medicine and treatment in other hospitals were not available. The impact of this on the result could not be ascertained. Furthermore, the assessment of renal dysfunction was based on the use of CrCl as eGFR calculated by using Cockcroft–Gault equation (which varies with age, weight, gender) without taking into consideration other determinants of renal function such as proteinuria and glucosuria from urinalysis. This could have skewed the incidence and prevalence of renal dysfunction. Considering these limitations, the study may not be generalisable to other healthcare centres.

CONCLUSION

In summary, this study lends further support to previous studies in Sub Saharan Africa that the incidence of renal dysfunction in patients initiated on TDF-based ART regimen is relatively low and transient in many cases. In view of this, it is recommended that the frequency of renal function monitoring in patients on TDF regimen be done within programmatic guidelines based on patients' risk factors and potential poor outcomes. Additionally, further studies that accurately assess the association between TDF regimen and renal dysfunction using more patients' covariates such as co-morbidities (i.e., chronic pain, hypertension, diabetes mellitus) and sensitive markers are recommended.

CONFLICT OF INTEREST

The author declares no conflict of interest in the conduct of this study.

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APPENDIX 1: DATA COLLECTION TOOL

AGE:

GENDER: MALE ☐ FEMALE ☐ OTHER ☐

HIEGHT:

	BASELINE	MONTH ON ARV					
		1	4	6	12	18	24
WEIGHT							
BMI*							
WHO Stage I							
Stage II							
Stage III							
Stage IV							
CD4							
VL							
Hb							
Creatinine							
eGFR							
Creatinine Clearance (CrCl)							
ARV: TDF							
FTC							
3TC							
EFV							
NVP							
AZT							
LPV/r							
Other: specify							
CO-MORBIDITY:							
(specify)							

*BMI= Body Mass Index

APPENDIX 2: UCT HREC APPROVAL LETTER

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone (021) 406 6626
Email: shurette.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

31 October 2017

HREC REF: 705/2017

Prof D Hellenberg
Family Medicine
Entrance 5, level 2
Falmouth Building

Dear Prof D Hellenberg

PROJECT TITLE: TENOFOVIR ASSOCIATED NEPHROTOXICITY IN ANTIRETROVIRAL THERAPY (ART) NAÏVE PATIENTS INITIATED ON TENOFOVIR BASED ART REGIMEN IN MITCHELL'S PLAIN CHC ARV CLINIC-(MMed-Candidate-Dr O Fayanju)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 31 October 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Dr Olanrewaju Phillips Fayanju will also be involved in this study.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 705/2017

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.