Tenofovir Experience from the Themba Lethu Clinic, Right to Care, Johannesburg.

Mulinda Nyirenda, MBBS(Mw), FCP (SA)

Student No: 0706998T

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DECLARATION

I, Mulinda Nyirenda, declare that this research report is my own work. It is being submitted for the degree of the Masters in Medicine, in the branch of Internal Medicine, at the University of Witwatersrand, Johannesburg – South Africa. It has not been submitted before for any degree or examination at this or any other university.

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Mulinda Nyirenda

20th Day of September, 2012

DEDICATION

To all HIV infected patients who show courage as they face life each day.

ABSTRACT

Background: Tenofovir use prior to its incorporation into the 2010 national guidelines is reviewed here.

Methods: This is a retrospective descriptive cohort study that reviewed de-identified clinical information and laboratory data of adult patients who received a tenofovir containing regimen as of 31st August, 2007 at Themba Lethu clinic, Johannesburg.

Results: Sixty naïve and 192 experienced patients received tenofovir containing regimens for a median (IQR) duration of 13 (7) months and 15 (10) months respectively. Weight gain, CD4 cell count gain and HIV RNA suppression were not significantly different between naïve and experienced patients. Creatinine was recorded for 155 (61.5%) patients. Mild renal dysfunction was common with minimal deterioration in NKF class. Only 3 patients developed NKF stage 4. Ten of 15 patients who died did not have renal function monitoring (X^2= 5.35; p = 0.02).

Conclusion: Tenofovir is effective and well tolerated, but screening for renal dysfunction is required.

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LIST OF ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral Therapy
ATV	Atazanavir
AZT	Zidovudine
BMI	Body mass index
CCMT	Comprehensive Care, Management and Treatment
CD4 cell count	Cluster of differentiation 4 cell count
CI	Confidence interval
DART study	Developing Anti- Retroviral Therapy study
d4T	Stavudine
DDI	Didanosine
EFV	Efavirenz
FTC	Emtricitabine
GFR	Glomerular filtration rate
HAART	Highly Active Antiretroviral Therapy
HIV	Human immunodeficiency virus
ICD 10	International Code of Diseases version 10
IQR	Inter-quartile range
LPVr	Lopinavir boosted with ritonavir
NKF	National Kidney Foundation
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OR	Odds ratio
PEPFAR	President's Emergency Provision for AIDS Relief
PI	Protease inhibitor
RCT	Randomized controlled trials
RNA	Ribonucleic Acid
RSA	Republic of South Africa
sd	Standard deviation
TAMs	Thymidine analogue mutations
TDF	Tenofovir disoproxil fumarate
WHO	World Health Organization

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CHAPTER ONE:

Introduction

This chapter will review the magnitude of HIV/AIDS epidemic in South Africa, outline the current national antiretroviral therapy program and review the present nucleoside reverse transcriptase inhibitor drugs available in the first line regimen. The chapter also contains a statement of the problem, justification of this audit, a literature review of tenofovir disoproxil fumarate (TDF) usage and the objectives of the audit. Unless otherwise stated, local experience refers to practices in force at the time of this study at Themba Lethu Clinic, Johannesburg (see section 2.2, Study Design).

1.1 BACKGROUND

1.1.1 Magnitude of HIV epidemic in RSA

South Africa has the largest HIV epidemic in the world. In 2010, approximately 5.24 million people were living with HIV in South Africa (1). The national HIV prevalence rate was reported at 10.5% (1). The most affected are adults aged 15–49 years, especially women (1-4).

The Gauteng province had an estimated HIV prevalence rate of11% in mid-2008 (2). Informal urban areas tended to have a higher overall prevalence than formal urban areas (2-4). The variable growth of epidemic in South Africa could be a result of a combination of factors like degree of urbanization, population demographics, sexual risk behavior, and /or unemployment (3).

1.1.2 Highly active anti-retroviral therapy in RSA

Highly active antiretroviral therapy (HAART) effectively treats HIV and has been available since 1987 in resource-rich countries. In South Africa, only a small minority could afford HAART in private healthcare until the introduction of the national

Comprehensive Care, Management and Treatment (CCMT) program in 2004. A national commitment thereafter has increased public access to HAART. At the end of 2007, it was estimated that only 27 percent of people in need of treatment were receiving it, below the average at the time for low and middle-income countries (5). By the end of 2009, this had increased to 56 percent, above the average for low and middle-income countries. However, these estimates are based on the previous WHO guidelines (6). The latest guidelines (2010) recommend starting treatment earlier, and have therefore increased the number of people estimated to be in need of HIV treatment, but the treatment coverage is only 37 percent (6).

Long term retention of patients on HAART is still challenging (7). The loss of patients on HAART has been attributed to death and stopping therapy, possibly due to side effects among other reasons (4, 8).

The goals of HAART are maximizing and maintaining suppression of viral load, restoration and preservation of immunologic function, improvement of quality of life and reduction of HIV related morbidity and mortality (9). In the CCMT program (until April 2010), patients were started on HAART based on the following criteria: 1) CD4 cell count less than 200 cells per mm^3 and symptomatic irrespective of stage of disease, 2) WHO stage IV AIDS defining illness irrespective of CD4 cell count; and 3) patient preparedness and readiness to take HAART adherently (9).

The HAART regimens that are used in the CCMT program were chosen based on a number of factors: potency, adverse effect profile, monitoring requirements, potential for maintenance of future treatment options, anticipated patient adherence, coexistent pregnancy, use of concomitant medications (i.e. potential drug interactions), potential for infection with a virus strain with diminished susceptibility to one or more antiretroviral drugs, availability, and cost (10).The South African HAART program is based on then

WHO guidelines with combinations of two treatment regimens: two nucleoside reverse transcriptase inhibitors (NRTI) in combination with either an initial non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimen or by a protease inhibitor (PI) based regimen (9-12) (Table 1.1). The initial first line regimen comprised of a NRTI backbone of stavudine (d4T) or zidovudine (AZT) if d4T is contraindicated or side effects develop, and lamivudine (3TC) in combination with NNRTI base of efavirenz (EFV) or nevirapine (NPV) (9).

1.1.2.1 NRTI in First Line Regimen Toxicity Profiles

1.1.2.1.1 d4T (Stavudine)

Stavudine has several features that make it the drug of choice for first-line antiretroviral therapy regimens in many resource-limited settings. It is effective, inexpensive and has a relatively mild short-term toxicity profile. This may encourage patient adherence. Unfortunately, long-term d4T use has been associated with mitochondrial toxicity leading to serious side effects including peripheral neuropathy, lipodystrophy and hyperlactaemia/lactic acidosis. These toxicities significantly affect the wellbeing and adherence of individuals on the first line therapy (10). In patients receiving d4T/3TC/EFV regimen at Themba Lethu clinic in Johannesburg; peripheral neuropathy, lactic acidosis and lipodystrophy had incidences of 8.7 per 100, 5.1 per 100 and 4.9 per 100 patient-years respectively. More than 50% of d4T treated patients required a switch due to mitochondrial toxicities (13). In the Khayelitsha cohort of the Western Cape, 21% of patients starting on a d4T based regimen required a switch to alternative antiretroviral therapy within three years because of toxicity (12). Indeed d4T is becoming less favored due to these long term toxicities (14).

I – Table 1.1: Outline of antiretroviral treatment regimens used in South Africa from 2004 to 2010

Regimen	Drugs	Indications
First line regimen	Stavudine (d4T) Lamivudine (3TC) Efavirenz (EFV)	Men Women on reliable contraception
Alternative First line regimen	Stavudine (d4T) Lamivudine (3TC) Nevirapine (NVP)	Conditions where EFV is contraindicated. Women who are unable to guarantee reliable contraception while on therapy. Pregnant women.
Second line regimen	Zidovudine (AZT) Didanosine (ddI) Lopinavir boosted with Ritonavir (LPVr)	Virological failure on the first line regimen

Adapted from Department of Health, 2004: National Antiretroviral Treatment Guidelines. First Edition.[6]

1.1.2.1.2 AZT (Zidovudine)

AZT often replaces d4T in antiretroviral combinations due to its more advantageous long-term tolerability profile. However, its use is associated with an increased risk of anemia and neutropenia in the short term (10).This is more common in our setting where patients are more likely to have cytopenias secondary to advanced HIV infection and associated opportunistic infections (15) making additional laboratory monitoring an added burden to ensure patient safety. AZT may also cause mitochondrial toxicity manifested as peripheral neuropathy and lipodystrophy (10).

1.1.2.1.3 3TC (Lamivudine)

3TC has established itself as a good adjuvant NRTI for d4T or AZT in HAART regimens. It has a good safety profile, although life threatening pure red cell aplasia may occur rarely (16). It is also effective against Hepatitis B virus (HBV); although resistance reports are increasing. Hepatic flares may occur in patients with dual infection and abnormal liver

function tests being commenced on the first line regimens. Since HBV/HIV co-infection rates have been estimated at about 5% in the South African setting (17), hepatic dysfunction with the use of 3TC is important.

1.2 STATEMENT OF THE PROBLEM

The use of d4T and AZT based regimens is already limited in developed countries (and a few developing countries) due to these associated toxicities. In the Western Cape of South Africa, Boulle et al report that treatment limiting toxicities (especially d4T related toxicities) are present and continue to accumulate with time; despite good tolerance of the initial HAART regimen in a high proportion of treatment naïve adult patient (12). This necessitated the need to substitute NRTIs in our initial HAART regimens (10, 12, 14).

Alternative nucleoside or nucleotide NRTI to d4T and AZT in a NRTI backbone are TDF and abacavir (ABC) (10). Both ABC and TDF have more favorable adverse effect profiles that AZT and d4T. The consideration of ABC, as an alternative first line regimen NRTI is limited mainly by its cost. The main side effect is a hypersensitivity reaction which is an idiosyncratic multi-system inflammatory reaction that includes fever, rash, gastrointestinal symptoms and malaise. On prompt termination recovery occurs, but subsequent re-challenge can lead to more severe and sometimes life threatening reactions (10). TDF is indicated in the treatment of HIV as a component of HAART in people aged 18 years or over (10).It has been added to the WHO guidelines in 2006 as one of the first line antiretroviral drug formulary. Since TDF is taken once daily at a dose of 300mg with or without food, it provides a better patient friendly profile and may improve adherence to HAART. It is preferred to older NRTIs as it is associated with fewer metabolic adverse effects (lipodystrophy and lactic acidosis) although nephrotoxicity is a concern. Randomized clinical trials and longitudinal studies from resource rich settings have found

clinically significant renal damage to be rare in those with normal baseline renal function (10).

1.3 JUSTIFICATION

The initial first line HAART regimens are proving to be problematic in terms of toxicities associated with d4T and 3TC use (10,12,14,18). This may result in poor patient adherence to therapy with poor outcomes of treatment.

TDF provides good virological suppression, continued CD4 cell count increase and fewer side effects. Currently, TDF is the favored possible alternative option to d4T. In addition, TDF has a potential to simplify HAART treatment by offering a simplified once daily regimen and a more favorable side effect profile that may facilitate the provision of treatment at the primary care level. At the time of this study TDF was not in regular use and there was no description of the South African experience with TDF. In this study, the opportunity was therefore taken to review the experience gained at Themba Lethu clinic where TDF was available in a PEPFAR supported program.

1.4 LITERATURE REVIEW

TDF is a NRTI that was approved for HIV infection in 2001.It was approved for public use in South Africa in mid-2007. But its availability was still restricted to research centers and the private sector; where it was a substitute for d4T or AZT. Public sector use was limited by its high cost in resource-limited settings. In South Africa its costs ranges from USD235 to USD195 (18). The new revised 2010 South African antiretroviral treatment guidelines have now included TDF as a component of the first line regimen instead of d4T for all new patients needing HAART (19).

1.4.1 TDF efficacy

TDF has shown its efficacy in clinical trials and occasional superiority in decreasing HIV RNA in both ARV naïve and treatment experienced HIV patients (20-24).

1.4.1.1 Virological Response

1.4.1.1.1 In patients with virological failure

Addition of TDF to failing HAART regimens in patients with confirmed virological failure may improve virological suppression. The phase II study GS902 showed significant decreases in HIV-1 RNA in the 54 patients who had TDF 300 mg added to their existing failing regimen. The average decrease in HIV-1 RNA from week 0 to week 24 was 0.58 log10 copies/ml ($p < 0.001$ vs. placebo), and was sustained through week 48 at 0.62 log10 copies/ml (23, 25). The phase III study GS907 also showed a statistically significant decrease in HIV-1 RNA in the 300 patients on TDF at 24 weeks (0.61 log10 copies/ml) versus those receiving placebo(0.03 log10 copies/ml, $p < 0.001$) (26). In Scandinavia, the efficacy of TDF in a clinical setting also proved its potency when added to a failing HAART regimen (27). These findings all confirmed that TDF was clinically potent in treatment experienced patients who are likely to have HIV drug resistant mutations (23).

1.4.1.1.2 In patients with d4T and AZT toxicities

When TDF was substituted for d4T due to d4T related toxicities in the GS903 study patients, sustained antiretroviral activity with continued immune recovery was seen through 6 years on treatment (21). In addition, patients had improved lipid parameters and limb fat compared to when they were receiving d4T. Virological control was also maintained if AZT was switched for TDF. An improvement of AZT related toxicities like

anemia was also seen (22-23). TDF showed better improvement of lipid profiles toxicities than ABC and was associated with fewer treatment-related discontinuations (23).

1.4.1.1.3 In Naïve Patients

Treatment naïve patients receiving TDF 300mg daily versus d4T 40mg twice a day sustained similar proportion of patients with sustained HIV viral load of less than 400 copies/mL at weeks 48, 96 and 144 (21-22). Naïve patients showed better viral suppression at 24 weeks (<400 HIV RNA copies) and at 48 weeks (<50 HIV RNA copies) on a TDF/ emtricitabine (FTC) NRTI backbone than on an AZT/ 3TC one (20).

1.4.1.2 CD4 cell count response

In the GS902 and GS907 studies, treatment experienced patients showed a greater portion of time weighted average CD4 cell count gain by week 24 of TDF use (10, 25-26). This CD4 cell count gain was maintained even at week 48 (26). In study 903, patients switched from d4T to TDF due to d4T related toxicities showed continued CD4 count increase while on TDF for 6 years. Naïve patients also show a good CD4 cell count increase on TDF, which was similar to that noted in patients on d4T (20-22). In the DART (Developing Anti-Retroviral Therapy in Africa) trial conducted in Uganda and Zimbabwe, 61% of 300 HIV treatment naïve patients receiving TDF plus AZT plus 3TC achieved a median CD4 count increase of 126 cells/mm^3 after 48 weeks (10, 28). This illustrated that TDF therapy in combination with other appropriate antiretroviral drugs effectively results in good immunological reconstitution in HIV patients.

1.4.2 <u>Anti-retroviral therapy combinations</u>

TDF's once daily dose is effective in treating HIV infection when used in a regimen containing more than one class and as part of a simplified dose regimen other than NRTI combination only (22). However, triple NRTI regimens containing TDF are not effective

and demonstrate high failure rates (29-30). The TDF/ddI/3TC combination showed virologic failure in 91% of study patients at week 12 (31-32). The TDF/ABC/3TC combination (with all drugs dosed once daily) has shown early virologic failure in up to 50% of study patients (29-30, 33). The weight of evidence indicates that triple NRTI regimens of TDF plus 3TC with ABC/ddI are not recommended.

The DART trial reported that AZT/3TC/TDF combination maintained good virological efficacy from 24 to 48 weeks in advanced HIV disease (28). AZT use with TDF may decrease the risk of developing K65R mutations associated with TDF resistance (34). Other triple NRTI regimens can include thymidine analogue and can be used only if an NNRTI- or PI- based regimen cannot or should not be used (35). Commonly used TDF combinations include TDF/FTC, TDF/3TC as the double NRTI component; in combination with either NNRTI (especially EFV) or PI boosted with Ritonavir (RTV) (20, 22-23).

1.4.3 TDF and drug interactions

Co-administration of TDF with ddI increases serum ddI levels; therefore dose-reduction of ddI is recommended (22, 31, 36). Co-administration of TDF with atazanavir (ATV) lowers serum ATV levels and increases TDF levels. TDF related toxicities are more likely to develop in such regimens. Renal dysfunction has been report in patients receiving TDF/ATV containing regimens (37-39). ATV levels should be boosted with low-dose RTV if used in combination with TDF (40-43). No other antiretroviral drugs have reported clinically relevant pharmacokinetic interactions and could be used as HAART combinations with TDF (22). TDF does not inhibit cytochrome p450 enzymes (22, 44); and can be safely administered with most concomitant medication used in HIV/AIDS care.

1.4.4 HIV Virus Resistance to TDF

Important resistance mutations for TDF described in the literature are the TAMs, K70E and K65R (22-23). NRTI cross resistance with thymidine analogues (d4T and AZT) is mainly seen in the presence of TAMs (M41L and L210). ddI, 3TC and ABC select the K65R mutation resulting in cross resistance. However cross resistance is not uniform, since TDF may remain susceptible in patients with reduced susceptibility to other NRTIs. This has made TDF as an accepted preference in salvage or second line therapy usage (23).

NRTI mutations present in the South African population have been described. Prior to the introduction of a national treatment program, a review of drug resistance profiles among 103 patients (39 children and 26 adults with HIV type 1 subtype C) that were virologically failing on HAART between 2000 and 2003 was done in Durban (45). Frequent NRTI mutations were M184V/I (37%), D67N (32%), T215Y/F (25%), K70R (21%), M41L (20%), K219Q/E (14%), and K65R (14%), reflecting the frequent use of 3TC and AZT (45). Data from Johannesburg clinics in 2008, also show that these mutations D67N (17.98%); M184V (64.29%); K70R (10.34%); K103N (42.86%); V106M (26.11%) and G190A (15.76%) were prevalent in our population as a result of the current HAART regimens used in the national roll-out program (46). The K65R (5.67%) and Q151M (4.43%) mutations had remained at similar frequencies as those reported in 2007. This could have been a result of minimal use of TDF in most clinics. The occurrence of both the NRTI mutations K65R and Q151M in our population may impact the use of TDF in our national rollout program (46). It is encouraging that HIV strains that have both K65R and Q151M mutations are more susceptible to TDF those with only the K65R mutation (22). The 903 study suggests that naive patients may have a reduced likelihood of having these resistant strains as less than 3% of the patients on TDF/3TC/EFV regimen developed

resistance to TDF over 144 weeks (47). This may suggest that treatment naive patients will have better susceptibility to TDF than treatment experienced patients.

1.4.5 Tolerability

TDF containing regimens seem to be well tolerated by both treatment experienced and treatment naïve patients (22-23). These tolerability profiles are similar to those of placebo and d4T containing regimens (21, 25-26). However, more favorable serum lipid profiles are seen on TDF use than d4T use (21, 27, 48). Mild GI disturbances are commonly reported. The prominent harmful side effect of TDF is renal toxicity that may manifest as renal dysfunction, Fanconi's syndrome and osteomalacia (49-50). Proximal renal toxicity is the underlining pathogenic mechanism (49, 51).

1.4.5.1 Renal dysfunction

Acute and chronic renal diseases are associated with HIV infection (52). Although HAART is altering the course of such HIV infection complications, TDF use has been associated with an increased incidence of renal dysfunction (53-57). Glomerular filtration rate (GFR) is said to decrease by 7-10 mL/min over 1 year in TDF treated patients with very small serum creatinine level increase to be identified as clinically significant (0.05 mg/dL) (10).

However, current data shows low incidences of TDF associated renal dysfunction that result in drug discontinuation (25-26, 39, 54-55, 58). In the African setting, the DART study recently showed that TDF was associated with minor impairments of kidney function with little clinical significance in a Zimbabwean and Ugandan population (59). In Zambia where TDF is used in the national rollout program, 10,485 adults initiated on HAART (66% on TDF, 23% on ZDV, 11% on d4T) experienced a non-statistically

different (p=0.51) mean change in creatinine clearance for TDF (-22.0mL/min) compared to AZT (–23.7 mL/min) and d4T (–22.8 mL/min) at 12 months (60).

Estimation of the GFR and serum creatinine evaluations at initiation of TDF helps predict patients who likely to develop renal dysfunction with TDF usage (54). Proteinuria is an another screening test for likely renal dysfunction that is a good predictive test for development of TDF associated renal toxicity (61). Monitoring for renal dysfunction in TDF use usually is done by monitoring the creatinine clearance and calculation of the glomerular filtration rate. However Woodward suggest that urine protein/creatinine ratio and serum phosphate monitoring is more indicative of renal tubular dysfunctional that occurs on TDF, than just a serum creatinine and a urine dipstick for albuminuria that are screening markers of glomerular disease (49).

Identifiable risk factors for development of TDF associated renal toxicities have been reported. Baseline renal dysfunction is an important risk factor (23, 37, 55). However treatment naïve patients with mild renal dysfunction (an estimated GFR of 50 to 80 mL/min (0.83 to 1.33 mL/s) by the Cockroft-Gault method) in Germany, UK and USA, had no more renal side effects on TDF through 96 weeks of follow-up than on a thymidine analog (d4T or AZT) (62). The magnitude of baseline renal dysfunction that is safe for TDF initiation is yet to be established. From a renal safety perspective, patients with GFR less than 60mL/min should not be initiated on TDF(63). In a British cohort, female sex and low baseline CD4 cell count were identified as risk factors for developing TDF associated renal toxicities (64). Some TDF-based HAART combinations like TDF/ddI and TDF/ RTV boosted protease inhibitors especially ATV, had a high risk of renal dysfunction (37-39). HIV-HBV co-infected patients with no prior renal impairment had low incidences of moderate renal impairment under TDF; and were not significantly different from those in the NRTI group (65). Other associated factors for the development

of renal complications on TDF containing regimens included low body weight, concomitant treatment with potential nephrotoxic drugs, prior HAART use, and an increased susceptibility in genetic polymorphism of renal tubular transporters (54-55).

1.4.5.2 Bone toxicity

TDF is a phosphonate that can be taken up by bone cells. Proximal tubule dysfunction associated with TDF can also result in phosphate wasting and Fanconi's syndrome that can increase the risk of bone demineralization (49). HIV patients receiving TDF containing HAART regimens have decreased mineral bone densities over time (21, 49).

The risk of decreased bone mineral density with TDF is yet to be established. Most studies that show decreased bone mineral density with TDF use have been done in young children and adolescents. It is possible that TDF bone loss may be increased during bone growth and development (51).

1.4.6 HIV – Hepatitis B Co-infection

The prevalence of Hepatitis B (HBV) is approximately 10 times higher in HIV infected patients than the general population and the risk of cirrhosis and liver disease related death increases in co-infected patients (66). The co-infection rate of hepatitis B/HIV as defined by hepatitis B surface antigen positivity is five times the prevalence of non HIV infected individuals in urban SA (17).TDF has potent antiviral activity against HBV (66-69). The safety and efficacy of the use of TDF in HBV and HIV co -infection has not been investigated thoroughly but is likely to be valuable as portrayed in small studies (69-70). Current guidelines suggest that treatment naïve patients co-infected with HIV and HBV should receive TDF/FTC NRTI backbone (23).

At the time of this study the use of TDF had not been described in South African patients other than in clinical trials. This study reviews the use of TDF in a single clinical practice

(Themba Lethu Clinic) before South Africa adopted TDF as part of the first line HAART regimen in 2010 and describes the experience of TDF use in treatment experience and naïve patients.

1.5 OBJECTIVES OF THE STUDY

1.5.1 Main objective

To describe the experience of the use of TDF in Themba Lethu clinic prior to the adoption of TDF as part of the national rollout program.

1.5.2 Specific objectives

1. To identify the indications for introducing TDF in patients on HAART.
2. To identify the current TDF regimen combinations used in our setting.
3. Quantify the CD4 cell count gain in patients on a TDF containing regimen, thus describing the immunological response on TDF regimens.
4. Review the virological suppression of HIV in patients on a TDF containing regimen.
5. Identify the clinical response of patients switched to TDF containing regimen.
6. To cite the occurrence of TDF related side effects noted in patients on TDF containing regimen for a year.

CHAPTER TWO: MATERIALS AND METHODS

Introduction:

In this chapter, the study design and methodology are presented. The study population is described and selection of the study sample is explained. The data collection system at the study site is described and details of the variables to be analyzed are presented. Definition of each clinical, immunological and virological outcome of interest is given and the chapter ends with a review of the data analysis plan and ethical consideration of this audit.

2.1 STUDY DESIGN

This was a retrospective descriptive cohort study conducted as a secondary data analysis of data collected from adult patients receiving antiretroviral therapy at Themba Lethu clinic.

2.2 STUDY SITE

Themba Lethu Clinic is a major urban site for implementation of comprehensive HIV and AIDS care, management and treatment in South Africa. It situated at Helen Joseph Hospital, a provincial public hospital in Gauteng province and is one of the biggest HAART centers in southern Africa. The clinic provides free antiretroviral therapy to more than 24,000 infected adults in Johannesburg and environs. The clinic is supported by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) through the United States Agency for International Development (USAID) through Right to Care, a nonprofit section 21 company with the goal of providing innovative and expert treatment for HIV and AIDS. This partnership enabled Themba Lethu clinic to be one of the first public sector clinic to offer TDF to patients who had contraindications or had developed side effects to d4T or 3TC since 2004 and before its registration by the Medicines Control Council of South Africa. It is for this reason that this site was considered appropriate for review of TDF use.

2.3 STUDY POPULATION.

As of 31st August 2007, 6,617 patients had been initiated on HAART at Themba Lethu clinic since its inception on 1st April, 2004. Two hundred and two patients were eligible for the audit.

2.4 STUDY CRITERIA

2.4 .1 Inclusion criteria:

- Patients older than 18 years of age at the time of the audit.
- Patients that had been started on a TDF containing regimen before 31st August, 2007.
- Patients with records of more than two visits in the Therapy Edge-HIV™ database, while receiving HAART.

2.4 .2 Exclusion criteria:

- Patients that were receiving TDF from the Right to Care pharmacy but were under the care of private practitioners. Although records were available on these patients they did not form part of the Themba Lethu database.

2.5 DATA MANAGEMENT

2.5.1 Data collection

At Themba Lethu clinic demographic and clinical patient information was recorded on an electronic database – Therapy Edge-HIV™. Data was collected from patient files after each clinic visit. At initiation of HAART, an "ARV initiation form" was used to collect baseline demographic, clinical and laboratory data. At every visit a patient has vital signs, weight, symptoms and new diagnoses were recorded on a "Follow-up Visit Form". Blood tests for CD4 cell count, HIV viral load, liver function tests and urea, creatinine and

electrolytes were done at each scheduled visit (four months after initiation and approximately every six month thereafter) and recorded on the database. Any clinically indicated additional investigations and results on "scheduled" and "unscheduled'' visits were also recorded on the database. All data was de-identified and unique study numbers were allocated to each individual before data was provided for analysis.

Before TDF was licensed for use in South Africa, the Right to Care (Right Med) Pharmacy in the Clinical HIV Research Unit had a consenting document that the clinician completed to identify the indication of using TDF as an unregistered drug for HAART. It also contained a section that provided standard information on TDF for the patient to know; and thereafter give consent of acceptance to use TDF. These documents were the initial source for a summary of diagnosis of patient, previous HAART regimen, concomitant diseases present in patient and their current treatment; and the indication for the switch to a TDF based regimen. The pages that had patient identification information were kept by the pharmacy and were not available to the investigator.

A data collection sheet was designed to act as a guide in the extraction of the information required from the database (Appendix 1).

All variables of interest were coded for analysis. Observation periods for weight measurements and laboratory data were divided into 4 month time intervals. Cross tabulation and frequency was done to ascertain internal consistency and validity of data using SAS version 9.1 (71) and Microsoft Excel software packages (72). The data was then exported to STATA software, version 10 for analysis (73).

2.5.2 Study variables

All definitions of study variables were established before data was analyzed.

2.5.2.1 Main variables of interest:

1. **TDF exposure:** any recorded use of TDF regardless of duration of exposure.
2. **Prior HAART regimen**: the starting HAART regimen in the treatment experienced patients regardless of the various changes in regimen before TDF was added.
3. **Current HAART regimen:** the HAART regimen that the patient was receiving as of 31st August, 2007.
4. **Baseline laboratory values** (CD4 cell count, viral load and creatinine clearance): identified as any result within 3 months to initiation of HAART regimen
5. **Baseline Weight**: any weight measurement within 1 month of initiation of HAART.
6. **Baseline conditions:** conditions (in particular opportunistic infections and malignancies) recorded within 3 months before initiation of HAART.
7. **TDF indication:** if not found in database or records, was inferred from conditions present within 3 months of starting a TDF containing regimen. They were coded as follows:
    a. Probable d4T/AZT toxicity : given to patients who had more than 2 regimen change
    b. Probable d4T/AZT contraindication: when TDF was used as a first line regimen.
    c. AZT toxicity/d4T contraindication: when prior HAART regimen had AZT as first NRTI choice.
    d. 3TC/AZT toxicity : if patient's HAART regimen included both d4T and TDF

e. Viral resistance: assumed if more than 3 HAART regimen changes were made and patient was currently on an unusual HAART regimen.

f. AZT contraindication: if immediate TDF substitution for d4T without use of AZT.

8. **TDF reason for discontinuation:** presence of known toxicity of TDF or none if it was not possible to establish a cause.
9. **HAART regimen change:** substitution of a single HAART drug.
10. **Creatinine clearance:** calculated using the Cockcroft-Gault equation (appendix 2).
11. **Renal dysfunction**: identified by an elevated creatinine clearance with an estimated GFR < 90 ml/min.

    Renal dysfunction was then graded according to the national kidney foundation (NKF) and the international network for strategic initiations in global HIV trials (INSIGHT) as:

    i. **Normal** if GFR > 90 ml/min: Stage 1
    ii. **Mild** if GFR = 60-89 ml/min: Stage 2
    iii. **Moderate** if GFR = 30-59 ml/min: Stage 3
    iv. **Severe** if GFR = 15- 29 ml/min: Stage 4
    v. **Renal failure**< 15 ml/min: Stage 5
12. **Viral load:** was measured using the HIV RNA detection method that had a minimum detection of 400 HIV RNA copies in 1mL of blood. Viral load observations were categorized as:

    Detectable = viral load ≥ 400 HIV RNA copies/mL

    Undetectable = viral load < 400 HIV RNA copies/mL

2.5.2.2 Other variables:

1. **Age** as of 31st August, 2007

2. **Race:** defined as Asian, Black, Colored or White.
3. **Height** measured at initiation of HAART, to calculate BMI; if not present then any recorded height measurement during care.
4. **Lost to follow up**: A patient who did not report for a clinic visit for 3 consecutive months. This status was confirmed if patient did not report to clinic for 6 consecutive months

2.5.3 Data quality control

The data at Themba Lethu Clinic is captured from medical records to an electronic database via medical management software- Therapy Edge-HIV^{TM}. The database is managed and maintained by Right to Care which through a team of trained data capturers, capture data electronically and do quality assurance check lists. Right to Care and the Clinical HIV Research Unit of the Department of Medicine (University of Witwatersrand) provided the researcher with a de-identified dataset containing the required fields of interest. Since the data was captured by data capturers from clinical notes and verification of data by the researcher was not possible due to de- identified nature of the data, observations with values which seemed implausible were set to missing by the researcher. Variables which were cleaned in this way included:

Height – plausible values were deemed to be between 135 and 200 centimeters.

Weight – plausible values were deemed to be between 30 and 200 kilograms.

CD4 cell counts – these are reported as integers by the laboratory and so values with decimal places were considered typing or capturing errors and set to missing.

Viral Load - these are reported as integers by the laboratory and so values with decimal places were considered typing or capturing errors and set to missing.

Serum Creatinine - plausible values deemed to be between 0.1 and 700 mg/dL.

Creatinine clearance - plausible values deemed to be between 0.1 and 500 ml/min.

2.6 DATA ANALYSIS

Statistical analysis was done using STATA statistical package, version 10.1 (STATA Corp., College Station, Texas). Statistical significance was ascertained at the 5% level of significance.

A comparison of baseline cohort characteristics of the naïve and experienced patients was done using the χ^2 test for categorical data and the Student ***t*** test for continuous variables. The Wilcoxon rank sum test was used to compare variables with non-normal distribution of CD4 cell counts. The Kruskal-Wallis test was used to test the difference in ethnicity, baseline WHO staging, current status of patient, reasons for discontinuation of TDF regimens and number of HAART regimen changes between naïve and experienced patients.

Weight, CD4 cell count, creatinine clearance and the log of detectable viral loads were tested graphically by histograms for normal distribution. The gain in weight, CD4 cell count, and log of detectable viral loads from initiation to 4, 8 and 12 months was calculated. The gain within the experienced or naïve patients was then tested using the paired t - test for significance. The mean difference of weight, CD4 cell count, and log value of detectable viral load at initiation, 4, 8, 12 and 24 months were calculated in order to compare the weight, virological and immunological response to TDF in treatment experienced and treatment naïve patients. The unpaired t-test was used to test the significance of the mean difference. The null hypothesis in significance testing for the mean difference was that there was no difference between the naive and experienced patients taking TDF. A comparison of the number of patients with detectable and undetectable viral loads between the naïve and experienced patients used the χ^2 test.

A missing data analysis was performed for key study variables: age, sex and prior ART usage. Significance testing was done using the Pearson chi squared test.

The occurrence of renal dysfunction at different time intervals was described using frequency tables. The odds ratio was used to identify the risk of developing renal dysfunction of NFK stage 2 or more between naïve and experienced patients; as well as the risk of death as an outcome in patients who had at least one creatinine measurement while taking a TDF regimen. The chi squared test determined the significance of the death outcome in relation to having a creatinine measurement being done while taking a TDF regimen. We then tested for association of prior HAART usage and development of renal dysfunction for age, sex, baseline creatinine clearance, baseline CD4 cell count, baseline weight and type of TDF combination using univariate and multivariate logistic regression. The Chi squared test was used to ascertain significance.

Data was then presented in tables, graphs and descriptive formats.

2.7 ETHICAL CLEARANCE

Personal identifiers of participants in this study were removed prior to data being given to the researcher. The researcher could not identify individuals in the sample or collect informed consent from the sample population. The study was conducted according to the Standard Operation Procedure (SOP) of the Clinical HIV Research Unit governing the analysis of data from the Themba Lethu Clinic which includes inter alia the approval of the research protocol by the University of Witwatersrand Committee for Research on Human Subjects (Medical). The protocol was approved by the Wits University Human Ethics Committee on 31st August, 2007 (protocol number M070821). Permission to conduct the audit was also obtained from the CEO of Helen Joseph Hospital where the Themba Lethu Clinic is based. The Postgraduate Committee of the Faculty of Medicine, University of Witwatersrand also approved the audit as a research report in partial fulfillment of the degree of Masters in Medicine in the specialty of Internal Medicine.

CHAPTER THREE: RESULTS

Introduction

This chapter will describe the findings of the audit according to the objectives of the study. The baseline characteristics will be outlined. The indications and TDF-HAART combinations used at Themba Lethu clinic will be stated. The chapter will end with describing the occurrence of renal dysfunction related to TDF use in this population.

3.1 POPULATION CHARACTERISTICS

According to the study criteria, 252 patients were eligible for inclusion into the audit. Sixty (24%) patients were naïve and 192 (76%) were experienced when starting a TDF containing regimen. Two hundred and ten (83%) of the patients were still on treatment. Fifteen patients (6%) had died; the cause of death was not known in 12 patients (80%) while 3 patients (20%) died of bacterial pneumonia, tuberculosis and cardiac failure. The base line demographic and clinical features in naïve and experienced patients were similar (Table 3.1). However, naïve patients had significantly lower mean (± sd) baseline weight (56.24 ± 11.92 kg) than the experienced patients (65.36 ± 12.30 kg) ($p = 0.02$).

II - Table 3.1: Demographic and baseline clinical characteristics of patients receiving TDF containing regimens.

Characteristic	Naïve		Experienced	
	N	Value	N	Value
Age (years) (mean+/-sd)	60	37.3 (9.92)	192	38.5 (8.91)
Sex:				
Female (n, %)	49	82%	143	74%
Male (n, %)	11	18%	49	26%
Ethnicity:				
Asian (n, %)	0	0	1	0.50%
Black (n, %)	57	95%	180	94%
Colored (n, %)	1	2%	7	4%
White (n, %)	1	2%	4	2%
Missing data	1	2%	0	0
Current Status:				
Alive on treatment	46	76.70%	164	86.90%
Dead	3	5%	12	6.30%
Defaulter	3	5%	4	2%
Lost to follow up*	6	10%	5	2.60%
Lost to follow up (confirmed)	2	3.30%	6	3.10%
WHO stage at HAART initiation:				
Stage 1 (n, %)	36	60%	103	53.65%
Stage 2 (n, %)	1	1.67%	1	0.52%
Stage 3 (n, %)	17	28.33%	62	32.29%
Stage 4 (n, %)	6	10%	26	13.54%
Height (centimeters) (mean +/- sd)	53	160.68 (7.44)	181	163.97 (9.21)
Baseline Weight (Kg) (mean +/- sd)	16	56.24 (11.92)	92	62.51 (14.90)
baseline CD4 cell count (cells/mm^3) (median, IQR)	11	111 (38-179)	15	209 (56 - 678)
Baseline HIV RNA levels ($\log_{10}$copies/mL) (median, IQR)	4	4.12 (2.72-5.20)	12	1.75 (1.69-3.08)
Baseline Creatinine Clearance (ml/min per $1.73m^2$) (mean +/- sd)	8	58.08 (20.36)	16	67.07 (17.37)

* Defined as: Missed visits for 3 months but unconfirmed status at 6 months from last visit.

3.2 PREVIOUS HAART USE PRIOR TO TDF USE IN TREATMENT EXPERIENCED PATIENTS

Of the experienced patients (n=192) who started HAART at Themba Lethu clinic prior to TDF use, 8 (4%) patients had already started HAART in private practice. Stavudine based HAART regimens were used in 163 (85%) of the experienced patients; mainly comprising of d4T+3TC+EFV. AZT based HAART regimens were mainly in combination with NNRTIs as a substitute to d4T (Table 3.2). Regimens not cited in the 2004 national guidelines were seen in patients who had started HAART in private practice. The median (IQR) duration on an initial HAART regimen prior to TDF use was 15.5 (5-25) months (Table 3.3). There was more than one HAART regimen change prior to using a TDF containing regimen in 79 (41%) experiences patients (Table 3.3). The most common regimen change was an NRTI substitution, usually between d4T and AZT.

III – Table 3.2: Prior HAART regimens used by treament experienced patients before starting a TDF containing regimen.

d4T based regimens	**n (%)**	**AZT based regimens**	**n (%)**
d4T+3TC+EFV *	121 (74%)	AZT+3TC+NNRTI	24(86%)
d4T+3TC+NVP *	20 (12%)	AZT+3TC+PI	2 (7%)
d4T+3TC+LPVr	9 (5.5%)	AZT+ddI+LPVr (2)*	2 (7%)
d4T+ddI+NNRTI	9 (5.5%)		
d4T+ABC+NNRTI	2 (1%)		
d4T+PI	3 (2%)		

* Regimens present in 2004 CCMT program guidelines as recommended first line HAART regimens
**Total number of experienced patients = 192, d4T based regimens=163(85%) and AZT based regimens =28(15%).

IV Table 3.3: A description of HAART use in naive and experienced patients

Characteristic	Naïve N (%)	Experienced N (%)	p-value
Initiated on HAART in clinic*			
Yes	60 (100%)	184 (96%)	0.11
No	0	8(4%)	
Still on TDF to date			
Yes	54 (90%)	171(89%)	0.84
No	6(10%)	21(11%)	
Reason for TDF discontinuation (n=27)			
Logistical decision**	0 (0%)	3 (2%)	0.42
None	6 (10%)	16(8%)	
Renal dysfunction	0(0%)	2(1%)	
Number of HAART regimen changes prior to TDF use $			
0	45 (75%)	0 (0%)	
1	9(15%)	79 (41%)	
2	4 (7%)	73(38%)	
>3	2(3%)	40(21%)	
Duration on HAART prior to TDF use in months ** * (median (IQR))	Not applicable	15.5 (5-25)	Not applicable
Duration of TDF usage in months (median (IQR))	13 (11-18)	15 (11-21)	0.37

*Initiated on HAART in Themba Lethu Clinic. For Naive patient, initiated on a TDF containing regimen
** Patients started on TDF in private practice but had no contraindication to d4T or AZT use. Themba Lethu clinic decided to stop TDF and put them on national regimens.
***All experienced patients had previous HAART regimen before a TDF containing regimen was started.
$ A substitution of a single HAART drug was taken as an ART regimen change.

3.3 TDF USAGE: INDICATIONS AND HAART COMBINATIONS

3.3.1 Indications for TDF usage

Indications of TDF use were categorized as those established and documented by clinician seeing the patient (definitive) and those that were established from data records according to clinical and laboratory data (inferred).

The common definitive indication for TDF use was the existence of severe peripheral neuropathy in 7 (12%) naive patients or the development of peripheral neuropathy on HAART in 65 (34%) experienced patients (Table 3.4). The development of NRTI mitochondrial toxicities, particularly in relation to prior d4T use were common in experienced patients. Hyperlactataemia and lactic acidosis developed in 28 (11%) of the experienced patients. Lipodystrophy was seen in 25 (10%) of the experienced patients. Anaemia was a common indication for patients who had been using AZT and had already developed d4T related toxicity. Established virological resistance and failure were also reasons for TDF use. The presence of HIV-HBV co-infection was also an indicator for TDF use. Two experienced patients were already on a TDF containing regimen when transferred from private practice and were maintained on the same regimen for logistical reasons.

Inferred indications in naïve patients showed that most patients were started on TDF due to presence of anaemia and/ or peripheral neuropathy at the time of initiating HAART. In experienced patients, stavudine toxicity, manifesting mainly as peripheral neuropathy, and/or the presence of anaemia secondary to AZT use were important.

3.3.2 HAART combinations used with TDF

The most common regimen was TDF+3TC+EFV (56%), followed by TDF+FTC+EFV (12.7%). The combination of TDF and ddI was used in 4 (1.6%) experienced patients who showed virological resistance to other NRTIs. TDF and ABC combinations as NRTI backbones were used by 5 (2%) experienced patients. TDF was used with ATV boosted with RTV in 1 naïve and 3 experienced patients (1.6% of the total number of patients). Only 2 (0.8%) patients were on a triple NRTI regimen (AZT+TDF+FTC, AZT+3TC+TDF).

V – Table 3.4: List of indications for TDF containing regimens in study population.

Indications	Naïve n	Experienced n	Total* n (%)
Definite indications **			
Peripheral Neuropathy	7	65	72 (29%)
Hyperlactataemia and Lactic acidosis	0	28	28 (11%)
Anaemia	6	22	28 (11%)
Lipodystrophy	0	25	25 (9.9%)
Failed regimen (virological)[$]	NA	16	16 (6.3%)
Viral resistance [$$]	0	8	8(3.2%)
Hepatitis B	0	5	5 (2%)
Pancreatitis	0	3	3 (1.2%)
Liver dysfunction	1	1	2 (0.8%)
Pregnancy	1	1	2 (0.8%)
Logistic[π]	0	2	2 (0.8%)
Hepatitis C	0	1	1 (0.4%)
Inferred indications***			
d4T and AZT contraindication	44	1	45(17.9%)
d4T toxicity and AZT contraindication	1	10	11 (4.4%)
AZT toxicity and d4T contraindication	0	4	4 (1.6%)

*Total number patients (n=252) in audit as denominator for %.
**Indications found in records
***Probable Indications inferred from conditions and laboratory results in patients with no documentation of TDF indication.
$ confirmed significant rise in viral load after previous suppression on HAART
$$ viral resistance testing done
Π logistic indication describes patients started on TDF containing regimens in private clinics before transfer to Themba Lethu Clinic

3.4 EVALUATION OF RESPONSE TO TDF

People with missing data were more likely to be experienced than naïve patients ($p<0.01$), in missing data analysis. There was no bias observed in relation to age or sex.

3.4.1 Immunological Response

The mean CD4 cell count gain over baseline was best seen between 8-12 months in both naïve and experienced patients (Table 3.5).The mean difference in CD4 cell count gain was not significantly different among the naïve and experienced patients (Table 3.6).

VI – Table 3.5: Tabulation of the mean change in measured parameters while using TDF containing regimens.

Parameter	Period of Observation	Naïve (n)	Experienced (n)	p- value*
CD4 Cell Count (cells/mL)	4 -8 months	35.16 (19)	46.23 (71)	0.68
	8 -12 months	125.66 (6)	56.24 (25)	0.47
Detectable HIV RNA (log 10 /mL)	4 -8 months	0.13 (2)	-0.06 (4)	0.60
Weight (kg)	0 -4 months	-2.83 (4)	1.08 (7)	0.01
	4 -8 months	2.86 (6)	-0.39 (83)	0.37
	8 -12 months	0.93 (3)	0.76 (66)	0.98

* The paired t-test of significance used to calculate the p-values.

VII - Table 3.6: Tabulation of the mean parameters observed while using TDF containing regimens.

Parameter	Period of Observation	Naïve mean (sd)	n	Experienced mean (sd)	n	P value)*
Weight (kg)						
	at initiation	56.24 (11.92)	16	65.37 (12.7)	16	0.05
	4 months	57.54 (8.96)	15	62.81 (13.84)	155	0.15
	8 months	59.35 (8.7)	6	66.68 (17.43)	86	0.31
	12 months	64.8 (8.91)	3	67.65 (15.5)	78	0.75
	24 months	60.5 (20.51)	2	67.37 (17.96)	37	0.6
CD4 cell count (cells/mL)						
	at initiation	128.4 (107.25)	15	305.55 (303.97)	11	0.05
	4 months	319.08 (179.98)	37	355.11 (205.40)	154	0.32
	8 months	373.6 (162.36)	20	394.12 (204.93)	81	0.68
	12 months	403.27 (219.33)	11	436.1 (220.27)	60	0.65
	24 months	262 (349.31)	2	456 (169.99)	12	0.2
Detectable Viral Load (log)						
	at initiation	4.55(1.14)	3	4.42(0.73)	3	0.56
	4 months	3.91 (1.10)	4	3.83 (0.88)	17	0.56
	8 months	4.16 (0.92)	4	4.41 (0.80)	6	0.16
	12 months	2.77 (0.24)	2	3.80 (1.07)	3	0.15

* The unpaired t-test of significance used to calculate p-values

3.4.2 Virological Response

The detectable viral load (log) data was normally distributed. There was no significant difference in the number of patients with detectable log of viral loads between the naïve and experienced patients at initiation, 4, 8, 12 and 24 months (Table 3.7). The mean difference in detectable log of viral load over 24 months was not significantly in both naïve and experienced patients (Table 3.6). Too few observations on changes in HIV viral load while using TDF were available to make meaningful observations.

VIII – Table 3.7: Distribution of patients with detectable viral loads while using TDF containing regimens.

Month	naïve			Experienced			p-value**
	n	Detectable*	Undetectable	n	Detectable	Undetectable	
At initiation	4	3	1	12	3	9	0.07
4 months	34	4	30	139	17	122	0.94
8 months	22	4	18	82	6	76	0.13
12 months	11	2	9	58	3	55	0.13
24 months	3	1	2	12	1	11	0.26

- *detectable if viral load ≥ 400 HIV RNA copies/mL
- **χ^2 test used to determine p-values

3.4.3 Clinical response

3.4.3.1 Weight response

The weight observations for the patients in this audit were normally distributed. At initiation the experienced patients had higher baseline weight values (mean 65.37kg) than the naïve patients (mean 56.24kg), with their mean difference being statistically significant (p =0.04). The mean weight gain was best seen in naïve patients between 4 to 8 months (2.86 Kg) while experienced patients showed an increase in weight within 4 months of starting TDF (1.08 Kg) (Table 3.5). The difference in mean weight after starting TDF

containing regimens was not significantly different in naïve and experience patients at 4, 8, 12 and 24 months (Table 3.6).

3.4.3.2 Prevalence of HIV related conditions before and after TDF use

Tuberculosis and opportunistic infections were the common HIV related conditions. The experienced patients had more cumulative tuberculosis, opportunistic infections and WHO stage 3 conditions (mainly oro-oesophageal candidiasis) on TDF containing regimens than when these patients were on their previous regimens. Most of these conditions were reported within 4 months of starting TDF containing regimens.

Patients reported with respiratory conditions frequently. Other medical problems included nonspecific pain and chronic rheumatologic and endocrine problems. Experienced patients on TDF also had more respiratory and abdominal problems reported prior to starting TDF than their naïve counterparts.

3.5 MONITORING TDF TOXICITIES

Patients started on TDF were monitored as defined by the clinic schedule. There were more missing follow-up laboratory results for experienced patients than the naïve ones. Full blood counts, urea and electrolyte measurements were done routinely at scheduled visits. Phosphate levels were not monitored. There was no evidence that urine dipstick test for proteinuria detection was being done. No bone scans had been ordered for any patient in this cohort.

3.5.1 Renal dysfunction monitoring as defined by creatinine clearance

The only data available for the assessment of renal dysfunction was the creatinine clearance as calculated from the serum creatinine. Serum creatinines were available for analysis in only 155 (61.5%: 36 naïve and 119 experienced) of the 252 patients on TDF. Only a single serum creatinine result was recorded during the study period in 113 (73%) of

these 155 patients. In 39 (25%) of these 155 patients the first serum creatinine was measured at greater than eight months after the start TDF. No other measurements of renal function, such as urinalysis, were recorded.

Table 3.8 shows the number of naïve and experienced patients in whom creatinine clearances were recorded (single and repeat measurements) and the number with evidence of renal dysfunction according to time on TDF. Baseline renal function was assessed in only 24 patients (9.5%: 16 naïve and 8 experienced) eight of whom had evidence of mild to moderate renal dysfunction prior to starting TDF. In only one of these patients was a follow up serum creatinine recorded and that after 16 months of TDF exposure (Figure 3.1). Within four months of TDF exposure a further 68 patients (27%: 19 naïve and 49 experienced) had serum creatinines recorded. Of these 35 (51%) had evidence of renal dysfunction. Thirty one had mild to moderate renal dysfunction while two had NKF stage 4 and two had stage 5 renal dysfunction. In only 10 of these patients was a follow up serum creatinine recorded and only one patient had further deterioration (Figure 3.1). After eight months of TDF exposure, 49 patients (11 naïve and 38 experienced) had a serum creatinine recorded. In 21 this was the only recorded creatinine result in the study period. Eighteen had evidence of renal dysfunction most of which was mild (83%). Similar patterns were recorded in the subsequent months. Of the 35 patients in whom only one serum creatinine result was recorded after eight months exposure to TDF, 11 (31%) had mild renal dysfunction with none having more severe stages of dysfunction.

IX – Table 3.8: Number of naive and experienced patients in whom creatinine clearance was recorded (single and repeated measurements) and the number with evidence of renal dysfunction according to time on TDF.

	Baseline		**4 Months**		**8 Months**		**12 Months**	
	Naïve	Experienced	Naïve	Experienced	Naïve	Experienced	Naïve	Experienced
Total	**8**	**16**	**19**	**49**	**11**	**38**	**1**	**26**
NKF 1	3	13	7	27	6	25	1	15
NKF 2	3	2	11	16	4	11	0	9
NKF 3	2	1	1	3	1	1	0	2
NKF 4	0	0	0	2	0	1	0	0
NKF 5	0	0	0	2	0	0	0	0
	16 Months		**20 Months**		**24 Months**		**28+ Months**	
	Naïve	Experienced	Naïve	Experienced	Naïve	Experienced	Naïve	Experienced
Total	**3**	**10**	**1**	**8**	**1**	**4**	**1**	**8**
NKF 1	2	7	0	4	0	2	1	4
NKF 2	1	3	0	3	0	1	0	3
NKF 3	0	0	1	1	1	1	0	1
NKF 4	0	0	0	0	0	0	0	0
NKF 5	0	0	0	0	0	0	0	0

National Kidney Foundation (NKF) Stages of chronic kidney disease based on calculated GFR (ml/min/1.73M^2): Stage 1 = >90 (normal), Stage 2 = 60-89 (mild), Stage 3 = 30-59 (moderate), Stage 4 =15-29 (severe) and Stage 5 =<15 (renal failure).

Overall, of the 155 patients in whom creatinine clearance was available 65(42%) had some degree of renal dysfunction at the time when serum creatinine was first measured (Table 3.9). In the majority (83%) renal dysfunction was mild (NKF stage 2), while seven (11%) had KNF stage 3, two NKF stage 4 and two NKF stage 5.

Experienced patients were at greater risk of having some degree of renal dysfunction compared to naïve patients. Confining the analysis to the first serum creatinine recorded regardless of the timing with respect to TDF exposure (155 patients; Table 3.9), experienced patients were twice as likely to have renal dysfunction (OR 2.4 ; 95% CI 1.1 – 5.1). Likewise, the mean creatinine clearance recorded was significantly higher in experienced patients compared to naïve patients (100.0 ± 32.4 and 89.7 ± 24.1: p = 0.04). Similarly, in the 24 patients in whom baseline serum creatinines were recorded, the risk of renal dysfunction was significantly higher in the experienced group (OR 7.2; 95% CI 1.1 – 48.5) and although the mean creatinine clearance was greater (99.2 ± 25.4 and 85.5 ± 30.4)

the difference was not significant (p > 0.2). While increased risk of renal dysfunction in experienced patients was also seen in patients in whom the first creatinine clearance was recorded at four (OR 3.1; 95% CI 0.9 – 10.1) and eight months (OR 1.4; 95% CI 0.2 – 8.1) the risk was not significant.

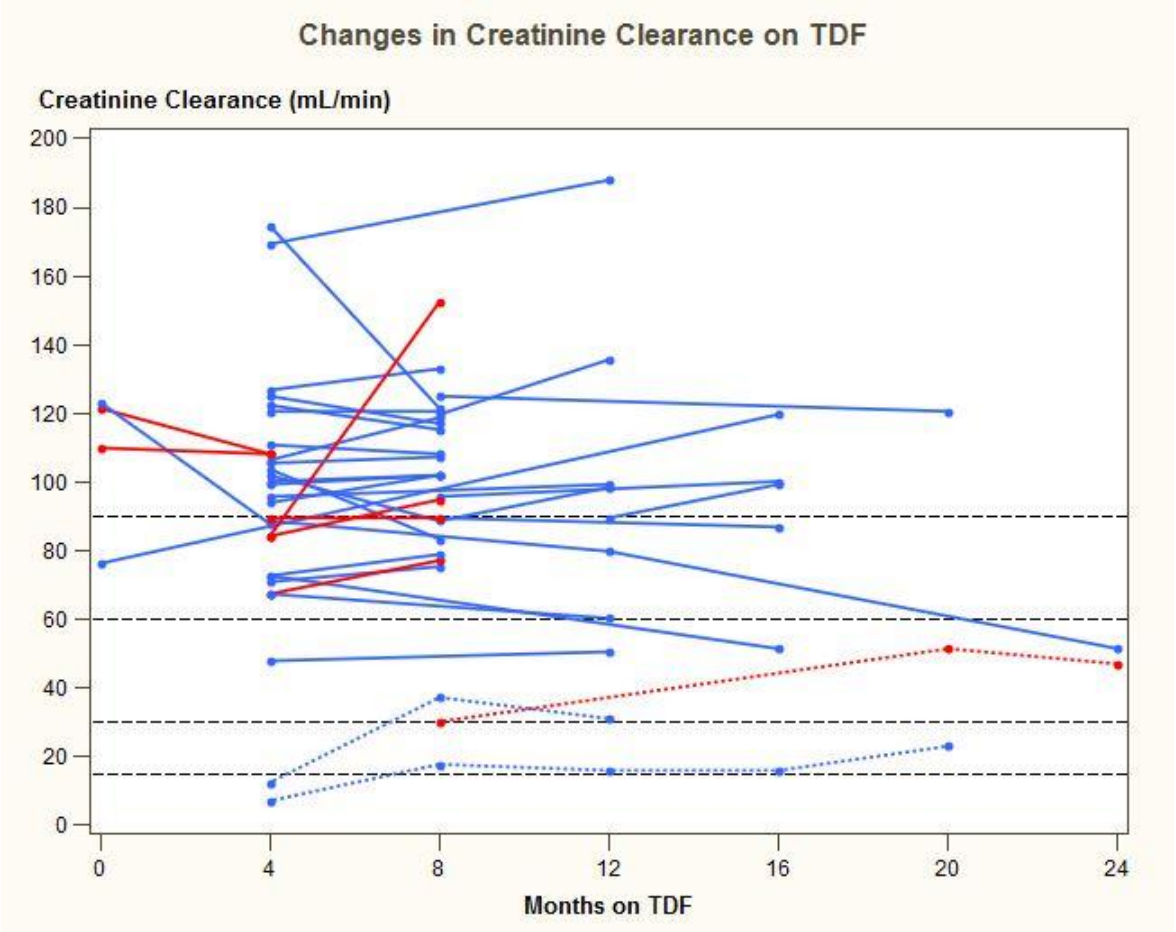
X -Table 3.9: Renal function in naïve and experienced patients (total 155) according to the first creatinine clearance recorded.

	Baseline		4 Months		8 Months		12 Months	
	Naïve	Experienced	Naïve	Experienced	Naïve	Experienced	Naïve	Experienced
Total	**8**	**16**	**17**	**48**	**7**	**20**	**1**	**17**
OR*	1	7.2 (1.1 - 48.5)	1	3.1 (0.9 - 10.1)	1	1.4 (0.2 - 8.1)	-	-
NKF 1	3	13	5	27	4	13	1	10
NKF 2	3	2	11	15	2	7	0	7
NKF 3	2	1	1	2	1	0	0	0
NKF 4	0	0	0	2	0	0	0	0
NKF 5	0	0	0	2	0	0	0	0
	16 Months		20 Months		24 Months		28+ Months	
	Naïve	Experienced	Naïve	Experienced	Naïve	Experienced	Naïve	Experienced
Total	**3**	**4**	**0**	**6**	**0**	**3**	**0**	**5**
NKF 1	2	4	0	3	0	2	0	3
NKF 2	1	0	0	3	0	1	0	2
NKF 3	0	0	0	0	0	0	0	0
NKF 4	0	0	0	0	0	0	0	0
NKF 5	0	0	0	0	0	0	0	0

National Kidney Foundation (NKF) Stages of chronic kidney disease based on calculated GFR (ml/min/1.73M^2): Stage 1 = >90 (normal), Stage 2 = 60-89 (mild), Stage 3 = 30-59 (moderate), Stage 4 =15-29 (severe) and Stage 5 =<15 (renal failure).
* Odds Ratio (95% CI). Risk of NKF stage2 and greater.

Figure 3.1 shows the changes in creatinine clearance seen with respect to time on TDF. Serial creatinine clearances were available in only 37 patients. In three, TDF was stopped when severe renal dysfunction was diagnosed; two at 4 months and one at eight months (Figure 3.1 dotted lines). All of these patients showed some improvement in renal dysfunction after stopping TDF. Deterioration in NKF class was seen in only three patients (all experienced). In one of these renal dysfunction deteriorated from NKF Stage 2 at four months to NKF 3 at 24 months but TDF was not stopped during the study period. In one naïve patient with moderate renal dysfunction at month eight (NKF class 3), creatinine

clearance improved on TDF. Of the 155 patients in whom creatinine clearance was recorded, five died and two were lost to follow up during the study period. Renal dysfunction was recorded within the first four months of starting TDF in six of these seven patients; five with mild (NKF stage 2) and one with moderate (NKF stage 3). The numbers were too small for statistical analysis.



Dotted lines represent patients in whom TDF was stopped (see text). The blue lines indicate experienced patients and red lines are for naive patients.

1 - Figure 3.1: Changes in creatinine clearance observed in individual patients while taking TDF containing regimens.

Fifteen of the patients died during the period of this review. Ten were in the group of patients in whom no serum creatinine had been measured compared to five in the group that had at least one serum creatinine measured (X^2= 5.35; p = 0.02). However, the risk of death in the group that had no measurements was increased although not significantly (OR 1.90 95% CI 0.92 – 3.91).

Factors associated with development of renal dysfunction were analyzed in a univariate analysis. Patients who had a baseline Creatinine clearance were protected from the development of renal dysfunction (OR =0.89, 95% CI = 0.81 - 0.99) Age, sex, baseline CD4 cell count, baseline weight, duration of TDF use and different TDF regimen combinations were not significantly associated with development of renal dysfunction (Table 3.10). Multivariate logistic regression was not possible with only one significant factor isolated.

XI – Table 3.10: Univariate analysis of factors associated with development of TDF associated renal dysfunction.

Parameter	**Odds Ratio**	**95% Confidence Interval**	**P-value**
Age	1.03	0.99 – 1.07	0.08
Sex	1.19	0.56 – 2.52	0.46
Baseline CD4 cell count	0.99	0.99 – 1.00	0.29
Baseline weight	0.91	0.83 – 1.00	0.05
Duration of TDF use	0.97	0.93 - 1.02	0.20
TDF combination	0.77	0.34 – 1.78	0.45

CHAPTER FOUR: DISCUSSION

This chapter reviews and explains the findings in the study. An analysis of possible biasness and limitations will be outlined. Suggestions for future studies will be given.

4.1 INTRODUCTION

We reviewed how TDF was used at Themba Lethu Clinic before its inclusion in the RSA Department of Health program. TDF containing HAART regimens were commonly used as alternatives to d4T or AZT regimens in treatment experienced patients who developed toxicities prior to its registration as an NRTI for HAART use in South Africa. This has been the typical indication for TDF in most HAART programs due to its high cost compared to d4T and AZT (18). Clinical, immunological and virological response to TDF containing regimens was observed to be good as reported in other studies (22-23). Limited monitoring for side effects was done on patients using these TDF regimens. While some TDF associated renal dysfunction was identified in this cohort, most was mild (NKF Stage 2). The finding was similar to that reported in the DART trial that observed patients in a similar setting as ours (28, 59).

4.2 REPRESENTATIVENESS OF THE STUDY POPULATION

The study provided an acceptable portrayal of the use of TDF at Themba Lethu Clinic and included all patients on the TDF containing regimen from the inception of the clinic till 31st August, 2007. A major restraint was the large amount of missing data pertaining to clinical findings, weight measurements, CD4 cell counts, HIV RNA and creatinine clearance measurements which suggests that protocols on the use of TDF had not been developed or were not followed. More experienced patients had missing data than naïve patients. The schedule of visits for treatment experienced patients is commonly less intense

than immediately following initiation of HAART. This may explain why experienced patients had fewer clinic visits than naïve patients despite the change in HAART regimens.

4.3 SYSTEMATIC OVERVIEW OF STUDY FINDINGS

4.3.1 Baseline Characteristics

The age distribution of our cohort captured the adult group (20-64 years) with the high prevalence rate in the country as reported in national statistics (2, 4). Female dominance in HAART clinics is commonly seen in sub-Saharan Africa (3-4, 74). HIV/AIDS is more common in the black race (4) and they are more likely to attend public institutions than the other races due to lower socioeconomic status.

Over half of the patients (53.7%) were asymptomatic (WHO stage 1) at initiation of HAART unlike cohorts in Cape Town who had advanced WHO stage 3 and 4 disease (12, 75-76). This may portray an increased uptake of voluntary HIV testing in the urban setting which may be attributed to higher education levels of the community or better health seeking behavioral patterns. However, other studies indicate that most patients get an HIV test while attending a general outpatient clinic even in urban settings (77). This finding however highlights the need for CD4 cell count testing to be done in patients with positive HIV test results as a gold standard guide for the patient to be initiated on HAART.

Naïve patients had low clinical, immunological, and virological parameters at the initiation of the TDF containing regimen. This is compatible with the characteristics of naïve patients starting on HAART nationally described in other studies (76-77). The experienced patients had better baseline parameters in response to their prior HAART use. The experienced patients with low baseline CD4 cell counts and high HIV RNA levels were patients who were failing on their previous HAART regimens.

4.3.2 TDF indications and combinations

d4T based regimens were used for at least one year on average (mean = 16 months) in our experienced patients. This was longer than observed in the Cape Town cohort (mean = 11 months) that required d4T based regimen substitutions due to development of d4T induced mitochondrial toxicities (12). The lack of appropriate substitute NRTI for d4T or AZT prior to TDF availability tended to result in at least two or more HAART regimen changes in both the Cape Town (12) and this cohort (Table 3.2).

Peripheral neuropathy is the most common contraindication or side effect that limits d4T use as a part of an HAART regimen especially in the first year of treatment (12, 14). HIV infected patients tend to have peripheral neuropathy attributed to HIV infection itself and other causes. Co-infection with tuberculosis in HIV infected patients is common both before and after initiation of HAART in our setting. Isoniazid associated peripheral neuropathy probably increases the incidence of peripheral neuropathy in patients on d4T containing regimens. Westreich showed that the risk of d4T substitution was increased among patients who received TB treatment and was especially elevated during the period soon after HAART initiation (78). TDF may be a good choice of NRTI in patients co-infected with TB and HIV who are likely to develop peripheral neuropathy with concomitant isoniazid and d4T use.

Hyperlactataemia and lactic acidosis cases (11%) were seen in our predominantly female cohort more frequently than in the Cape Town cohort (4.7%) (12). Women are identified as high risk group of developing this toxicity while taking d4T (12, 14, 79).

Lipodystrophy is a long term complication of d4T as such was not very frequent since few patients were on d4T for more than 2 years.

Anemia is common in HIV patients with advanced disease as a result of HIV effects on the bone marrow and also the presence of coexisting co-infections like TB that cause bone

marrow suppression. This was the common contraindication for AZT use. Anemia is likely to develop early in AZT use, resulting in need for its substitution (14).

As TDF availability becomes easier, its preferential use in an initial HAART regimen in naïve patients who have background peripheral neuropathy and anemia is likely to increase.

HIV- HBV co-infection is likely indication for a TDF containing regimen in a patient, since both infections are then treated concurrently (70). The TDF/FTC combination should be used in such cases so that 3TC resistant HBV strains are properly treated (23, 66, 70). Our current co-infection prevalence (approximately 5%, (17)) may be sufficient for this indication for TDF use to be cost effective in the national rollout program.

Current use of TDF in combination with other HAART was similar to that recommended in the literature. Unusual combinations were guided by viral resistance and susceptibility testing.

4.3.3 TDF efficacy

Good immunological, virological and clinical responses to TDF containing regimens were seen in this cohort. There was no significant difference noted in the responses between naïve and experienced patients taking TDF containing regimens. This study confirms the practical value of TDF as an initial or substitute NRTI in HAART seen in the literature (22-23).

4.3.3.1 Immunological response.

Immunological recovery in naïve patients was noted to be similar at 12 months on TDF to that seen in the sub-Saharan cohort of the DART study (10). Experienced patients also showed CD4 cell count recovery as seen in other cohorts (25-27).

4.3.3.2 Virological Response

Our cohort showed good HIV RNA suppression while taking TDF containing regimens. The larger magnitude of change in viral load noted in the naïve patients than the experienced patients may not signify better virological response in the naïve patients since experienced patients may have already had some virological suppression on their previous regimens. Virological suppression noted at 8 to 12 months on treatment in naïve patients suggests similar TDF efficacy reported in other studies at 24 and 48 weeks (21, 23). The sustained virological suppression in the experienced patients indicates its effectiveness as a substitute therapy in our setting. This efficacy is observed in spite of the increased presence of resistance mutations in our population (22-23, 46). The 903 study did indicate minimal risk of development of resistance in naïve patients (47). This reduces fear that widespread TDF use as a component of the first line regimen may propagate increase in NRTI-resistant HIV strains in our population.

4.3.3.3 Clinical Response

Clinical monitoring of HAART response in HIV patients is an important aspect of national rollout programs in rural settings where laboratory support is limited (80). Weight and the occurrence of opportunistic infections were the only clinical features available for analysis.

4.3.3.3.1 Weight Gain.

Assessment of weight gain is a simple tool to monitor HIV infected patients on HAART. It is of great use in decentralizing HIV care in areas with limited well trained physicians (81). Weight gain has been associated with greater survival on HAART even after 3 months of HAART use (81). Great median increases in body weight have correlated well with achieved virological suppression in patients (82) making weight gain a sensitive tool for assessment of HAART efficacy. However, its precision in reflecting HAART response is hampered by many factors that limit its precision and utilization in practice (83). This

clinical observation is still useful to less skilled health workers for identifying patients who need to be referred for expert review and laboratory tests like CD4 cell count and HIV RNA levels during treatment. In this cohort, weight increase was noted in all patients. Although the weight increase was not significantly difference between naïve and experienced patients, the naïve patients did have better weight gains than the experienced patients after 4 months. This is supports literature descriptions of weight increase on HAART being best seen after 6 months of HAART initiation (80, 83). The experienced patients may have already achieved their maximum weight gain on their initial HAART regimens. It would have been interesting to describe the weight gain pattern of experienced patients who had failed on prior HAART use and were now responding well on TDF containing regimens. The absence of weight observations for some patients during follow-up compromised detailed analysis for extrapolation of trends.

4.3.3.3.2 HIV related Conditions on HAART

Resource limited settings have compromised abilities to diagnose opportunistic infections in patients with HIV infection prior to HAART initiation and post HAART initiation. Identification of opportunistic infections in the first 3 to 6 months of initiating HAART usually does not signify HAART failure but rather reveals immune reconstitution syndromes (IRIS) (76, 80). Tuberculosis is the most common IRIS that occurs after 4 months of responsive HAART therapy in our setting (84-85). So the appearance of clinical tuberculosis cases after 4 months of TDF regimens in the experienced as well as in naïve patients possibly reflects an improved immunological status in the patients while on treatment. The IRIS phenomenon tends to be common in patients with low baseline CD4 cell counts (<200 cells/uL) (88). This may account for the opportunistic infections observed in this cohort after initiating TDF containing regimens. However opportunistic

infections after 6 months on HAART do suggest HAART failure and should prompt virological failure assessment. This was not observed in our cohort.

4.3.4 Monitoring for TDF Side effects

Several tests for monitoring TDF major side effects were not routinely recorded for this cohort. Tests like urine analysis, phosphate level, which are frequently used (86), were not done routinely and were therefore not available for analysis of the more unusual side effects of TDF. Current data from sub-Saharan Africa does suggest minimal incidence of side effects related to TDF use (59-60).

4.3.4.1 TDF associated Renal Dysfunction

There appeared to be no routine policy for clinicians to monitor creatinine clearance in patients receiving TDF containing regimens at Themba Lethu Clinic during this audit. Only a few patients (24) had baseline serum creatinines and most measurements were done at four or eight months. While serum creatinine measurements may have been done for other clinical reasons, it is likely that these late measurements were related to the realization that TDF has nephrotoxic potential. Accepting these reservations, the audit provides a reasonable, although inadequate, picture of the prevalence of renal dysfunction in patients receiving TDF in the clinic. Although the numbers are small, the fact that there were significantly more deaths in those patients where no monitoring of renal function was performed is of concern.

Mild renal dysfunction was common in naïve and treatment experienced patients prior to and during the first few months after starting TDF containing regimens. The cohort had many well described risk factors for underlying renal disease in HIV infected individuals including black ethnicity, low CD4 cell counts, high viral load and female gender (63, 87-89). As observed in other studies, mild renal impairment dominates while severe renal

impairment was rare (59, 89-91). The prevalence of HIV related renal disease prior to HAART use has not been determined in our setting. In Zambia 33.8% of 25,779 individuals starting HAART had renal impairment (90). The audit prevalence of 65.2% identified in this study (5 of 8 naïve patients) needs to be validated with a larger cohort.

The administration of TDF containing regimens in patients with baseline renal dysfunction is not unique to this cohort. As observed by Staszewski (62), baseline mild renal dysfunction in patients starting TDF containing regimens did not necessarily predict the occurrence of TDF associated renal dysfunction in both naïve and experienced patients. However, this should not undermine the prudence of avoiding starting TDF containing regimens in patients with GFR < 60ml/min as recommended by Winston (54).

In the relatively few patients in whom serial measurements were made (figure 3.1) this cohort demonstrated no significant decline in GFR while taking TDF containing regimens as observed in other studies. This finding is interesting since some reasons that contribute to GFR decline in HIV patients on HAART were identified in this cohort (63, 86, 88-89, 92). Naïve patients had advanced HIV disease with prevalent opportunistic infections, low CD4 cell counts and high baseline HIV RNA viral loads that all increased the known risk of developing acute kidney injury in the first year of HAART initiation (93). HAART experienced patients with advanced HIV/AIDS have high prevalence of both clinically evident chronic kidney disease and subclinical renal pathology (94). Prior HAART use, presence of opportunistic infections and concomitant use of RTV boosted PIs in experienced patients also increased their risk of acute kidney injury (93). These factors may have contributed to more renal dysfunction events in experienced patients. This finding is inconclusive since few creatinine clearance measurements were available for analysis. Severe GFR decline has been associated with acute inter-current illness rather than ongoing drug toxicity in patients taking HAART (63, 95-97). In this study, it was

difficult to establish if the decrease of GFR was associated with inter current illness or concurrent use of nephrotoxic drugs other than TDF that may have precipitated acute renal dysfunction as observed in the DART trial (59).We could not establish the presence of chronic kidney disease secondary to age related chronic diseases like diabetes and hypertension in this cohort.

The measurement of GFR is not specific for proximal tubular dysfunction that is well described as the pathology in TDF related nephrotoxicity (86, 92). Urine dipstick measurement for proteinuria and isosthenuria (specific gravity of urine = 1.010), as well as microscopy for casts suggest drug related renal dysfunction (86, 92). Unfortunately, these tests were not done in the Themba Lethu cohort making it difficult to differentiate glomerular dysfunction unrelated to TDF nephropathy. This was further compounded by few patients having baseline and follow up serum creatinine measurements.

The cohort had many risk factors for the development of TDF related nephrotoxicity. The early development of TDF associated renal dysfunction in the naïve patients may be attributed to lower baseline weight and baseline CD4 cell counts (54-55, 64). Prior HAART exposure may predispose to development of severe TDF associated renal dysfunction as observed in other studies (54-55). The risk of renal dysfunction, albeit mostly mild, was greater in this cohort if there had prior exposure to HAART. In the relatively few patients in whom serial serum creatinine were measured there was little indication that renal function deteriorated during the study period. However, this period may not have been long enough to show an increase in the incidence of TDF associated renal dysfunction with prolonged use of TDF noted by other researchers (54-56). The predominance of the female gender and black ethnicity may have increased the incidence of renal dysfunction in our cohort as described by Crum-Cianflone (87), although could not be appreciated in the regression analysis. Advanced age has been reported as a risk factor

for the development of TDF associated renal dysfunction (23, 87). There were few patients on TDF/ddI and TDF/ RTV boosted ATV regimens to establish their association with development of TDF associated renal dysfunction as reported in literature (36-38).

The findings in this study highlight the need to screen for glomerular and tubular dysfunction in HIV patients before starting on TDF containing HAART regimen in spite of reported low incidence of TDF renal toxicity. Although the risk of TDF renal toxicity clearly exists, the risk of greater renal dysfunction when HIV infection remains untreated cannot be ignored (92). HIV patient care should include risk stratification that highlights described risk factors for TDF related nephrotoxicity, vigilant management of opportunistic infections and concomitant conditions and nephrotoxic medication that may result in kidney injury in patients taking TDF.

4.4 POTENTIAL STUDY BIAS

More experienced patients had missing data than naïve patients. This may have undermined the magnitude of efficacy outcomes and incidence of renal dysfunction in the experienced patients.

Selective introduction of TDF containing regimens to naïve patients in the clinic may have been influenced by other health or socio-behavioral factors that were not reflective of the actual severity of conditions contraindicating other NRTI use.

4.5 GENERALIZABILITY

Themba Lethu clinic is a specialized HIV care clinic that has extra funding other than provincial or department of health funding. This results in more funds available for expert personnel and laboratory facilities which may not be available in other health facilities in South Africa. HAART experienced patients with advanced HIV/AIDS have high prevalence of both clinically evident CKD and subclinical renal pathology.

Simpler approaches to safe TDF use in such setting may be needed.

4.6 STUDY STRENGTHS

The review of routine clinical care best portrays standard daily practice of care than predesigned studies as resources are utilized according to normal settings. While the Themba Lethu Clinic is better resourced than most South African public sector clinics, the study does provide a window on experiences with TDF in South Africa.

4.7 STUDY LIMITATIONS

The use of retrospective data that is not designed for operative research has inherent limitations. The small sample size may have reduced the power to identify the actual incidence of TDF associated side effects like renal dysfunction. A major limitation was the amount of missing clinical information in the database downloaded from the Therapy Edge-HIV^{TM}. Logistical constraints may have influenced the entry of data in the Therapy Edge database, thus delaying entry of data collected at clinic visits and laboratory results for patients in this cohort. This limited the ability to isolate confounding and risk factors that were playing a role in the development of TDF associated renal dysfunction. Data on the reasons for discontinuation of TDF for most patients in this cohort was not available. Other socio- behavioral factors that influence TDF use in our setting could also not be described nor could the impact of TDF on the quality of life of the patients be established with the available data. Adherence to TDF containing regimens that may affect efficacy could not be described adequately.

4.8 SUGGESTIONS FOR FURTHER STUDIES

In view of the findings in this study and current developments in HAART care worldwide, there is need to identify factors that may affect the use of TDF in our setting by focusing

on the following issues:

1. Identification of risk factor for the development of TDF associated renal dysfunction.
2. The frequency and affordable methods of monitoring renal dysfunction while using TDF in our setting.
3. Incidence and monitoring required for bone related TDF toxicities

CHAPTER FIVE: CONCLUSION AND RECOMMENDATIONS

5.1 CONCLUSION

In conclusion, the results of this study have to be seen in the context of the time period during which the data was collected, April 2004 to August 2007. Since 2010, TDF has been included in the South African guidelines which include protocols for monitoring TDF usage (19).The study indicates that the use of TDF containing regimens as an HAART option in treatment naïve and experienced patients in a South African public clinic is effective and well tolerated. Tenofovir was used mainly as a substitute for d4T toxicities in experienced patients. Naïve patients were more likely to get an initial HAART regimen containing TDF if a d4T or AZT contraindication is present. TDF was commonly utilized in combination with 3TC as the NRTI backbone and EFV as the NNRTI option. This makes it a suitable choice to replace d4T in our current first line regimen. The limitation to widespread use of TDF previously has been its cost; estimated at $50.03 for a TDF/3TC/EFV combination compared to $36.65 for the current first line regimen – d4T/3TC/EFV (95). However, a recent study had shown that replacing d4T with TDF would be cost effective in the long term (18). It is with this perspective in mind that the South African Department of Health now recommends TDF + 3TC/FTC + EFV or NVP as the first line regimen for all naïve patients being initiated on HAART from 2010 (19). Evidence based, vigilant and uniform algorithms for monitoring TDF associated toxicities and resistance patterns throughout the country are needed.

5.2 RECOMMENDATIONS

There is still a need to define relevant safe indications for TDF use in patients presenting renal dysfunction at initiation, to maintain good clinical practice in the public sector. It is paramount that all patients have an estimated creatinine clearance measurement at initiation of TDF based regimens. Renal dysfunction associated with TDF use should be

monitored vigilantly. Currently, a comprehensive biannual renal function work up that includes GFR estimation by creatinine clearance, estimation of the urine protein/creatinine ratio and measurement of phosphate levels may be sufficient in our setting.

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APPENDICES:

Appendix 1: Data collection tool

Study ID No:……

1. Gender

Male		Female	

2. Race

African		Colored		Asian		White	

3. Age _____ years.

4. Height: _____ cm.

5. Weight pattern on ART:

Timing of weight measurement	**Weight in Kg**
before ART	
after 4 months of initial ART regimen	
at 10 months on initial ART	
At switch to TDF containing regimen	
After 6 month on TDF containing regimen	
After 12 month on TDF containing regimen	

6. WHO Clinical stage on onset of ART:

1	2	3	4

7. Opportunistic infections and malignancies noted before ART:

_____.

_____.

_____.

8. Concomitant medical conditions:

_____.

_____.

_____.

9. Initial ART Regimen:

D4T, 3TC, EFV	1	D4T, 3TC, NVP,	2	AZT, 3TC, EFV	3	AZT, 3TC, NVP	4	other	5

If other, indicate regimen: _____.

10. Duration of above ART regimen: _____ months.

11. Complications encountered:

Peripheral neuropathy	1	Lactic acidosis	2	Hyperlacta-emia	3	Anemia	4	hepatitis	5	other	6

Describe other: _____.

12. Medical conditions noted on initial ART regimen:

_____.

_____.

_____.

13. Indication noted for Tenofovir containing regimen:

Peripheral neuropathy	1	Lactic acidosis	2	Hyperlacta-emia	3	Anemia	4	other	5

Describe other:…….
……

14. Current regimen:

TDF, 3TC, EFV	1	TDF, 3TC, NVP,	2	other	3

Outline other TDF containing Regimen _____.

15. Duration Of regimen (months);

0 - 3		4 – 6		7 – 12		13 - 18		19 - 24		25 -above	

16. Medical conditions noted on TDF containing regimen.

_____.

_____.

_____.

17. CD 4 count:

a. before ART:

0-50		51-100		101- 150		151- 200	

b. after 4 months of initial ART regimen:

0-150		151- 250		251- 350		351- 450		>451	

c. after 10 months of initial ART regimen:

0-150		151- 250		251- 350		351- 450		>451	

d. At switch to TDF containing regimen.

0-150		151- 250		251- 350		351- 450		>451	

e. After 3 months on TDF containing regimen.

0-150		151- 250		251- 350		351- 450		>451	

f. After 6 months on TDF containing regimen.

0-150		151- 250		251- 350		351- 450		>451	

g. After 12 months on TDF containing regimen.

0-150		151- 250		251- 350		351- 450		>451	

18. Viral load monitoring:

a. before ART:

<400		400 – 1000		1000- 9000		10,000- 100, 000		>100,000	

b. at 4 months after initial ART:

<400		400 – 1000		1000- 9000		10,000- 100, 000		>100,000	

c. at 10 months on initial ART:

<400		400 – 1000		1000- 9000		10,000- 100, 000		>100,000	

d. At switch to TDF containing regimen:

<400		400 – 1000		1000- 9000		10,000- 100, 000		>100,000	

e. After 6 months on TDF containing regimen.

0-150		151- 250		251- 350		351- 450		>451	

f. After 12 months on TDF containing regimen.

0-150		151- 250		251- 350		351- 450		>451	

19. Laboratory results monitored and investigations done during Tenofovir use :

a. Full Blood Count

Yes		No	

Frequency of test:_____.

Test	Abnormality noted	Duration of Tenofovir Treatment (months)	Action taken	Frequency of occurrence
WBC (Total				
RBC				
Hemoglobin				
Hematocrit				
MCV				
MCH				
MCHC				
RDW				
Platelet Count				

b.Urea, Creatinine & Electrolytes

Yes		No	

Frequency of test:_____.

Test	Abnormality noted	Duration of Tenofovir Treatment (months)	Action taken	Frequency of occurrence
Urea				
Creatinine (Serum)				
Sodium (Serum)				
Potassium (Serum)				
Chloride (Serum)				
CO2 (Serum)				

c. Calcium ,Magnesium and Phosphorus

Yes		No	

Frequency of test:_____.

Test	Abnormality noted	Duration of Tenofovir Treatment (months)	Action taken	Frequency of occurrence
Calcium (serum)				
Magnesium (Serum)				
Phosphorus (Serum)				

d.Urine dipstick test

Yes		No	

Frequency of test:_____.

Test	Abnormality noted	Duration of Tenofovir Treatment (months)	Action taken	Frequency of occurrence
Protein				
Glucose				
Blood				
Nitrites				
Leucocytes				

e.Bone scan request

Yes		No	

Frequency of test:_____.
Abnormality:

Appendix 2: Creatinine Clearance Calculation.

The Cockcroft-Gault Equation:

For men:

$$\frac{(140\text{-age}) \times \text{weight} \times 1.23}{\text{Creatinine [micromol/l)}}$$

For women:

$$\frac{(140\text{-age}) \times \text{weight} \times 1.23 \times 0.85}{\text{Creatinine[micromol/l]}}$$

Appendix 3: Ethical Clearance Certificate.

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

Approved at the meeting

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Nyirenda

CLEARANCE CERTIFICATE **PROTOCOL NUMBER M070821**

PROJECT	The Review of Tenofovir in the South African Public Sector
INVESTIGATORS	Dr M Nyirenda
DEPARTMENT	Dept of Internal Medicine
DATE CONSIDERED	07.08.31
DECISION OF THE COMMITTEE*	APPROVED subject to reviewing cases till the end of August 2007 and using only the study number and not the file reference number

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

DATE 07.09.03 **CHAIRPERSON** .....
(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr C Menezes

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES