Rates of Switching First-Line Antiretroviral Regimen Tenofovir-Emtricitabine-Efavirenz combination in a Primary Care Service in South Africa

MMed(Family Medicine) Thesis

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DECLARATION

I, **David Huang**, 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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Literature Review

South Africa has the largest HIV epidemic in the world. With 7.2 million adults and children living with HIV, South Africa accounts nearly 20% of World's HIV population. The country also has the largest treatment programme in the world, accounting for 20% of people on Antiretroviral therapy (ART) globally and has one of the largest state-funded programmes, with about 80% of the ART funded by the government.[1]

The fixed Tenofovir(TDF)-Emtricitabine(FTC)-Efavirenz(EFV) drug combination (TEE) antiretroviral therapy (ART) was introduced to the South Africa public health sector around April 2013, whereas in the Western Cape Province the combination drug became available earlier since 2010. The South African national treatment guidelines have since stipulated this TEE as first line regimen for treating adult populations living with HIV-1 virus infection[2].

To date TEE is the most convenient dosing ART (one tablet taken by mouth daily) used in the Public Sector Health Services. The Emtricitabine and Tenofovir components have both shown good tolerability[3] over many years, with the efavirenz-component demonstrating virologic efficacy that is non-inferior to the protease inhibitor Lopinavir-ritonavir [4], one component of second-line regimens in South Africa.

Recent evidence has shown more detrimental and long term adverse effects of Efavirenz than previously known, including neuro-psychiatric (encephalopathy and increased suicidality) and metabolic adverse effects such as dyslipidaemia and impaired glycaemic control[5,6,7]. This data has prompted reconsideration of the role of EFV as first-line ART. Tenofovir disoproxil fumarate (TDF), although generally well tolerated, is known to have renal side effects.

The advent of integrase inhibitors, including Dolutegravir (DTG), which show superior efficacy to Efavirenz, has led to the World Health Organisation (WHO guidelines 2016) and several Southern African countries replacing EFV in first-line regimens with DTG. DTG is expected to be available widely in South Africa, as part of first-line ART, from February 2020.[8]

The global target to end the HIV epidemic by 2020 is called 90-90-90 : 90% of all people living with HIV will know their HIV status; 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy; and 90% of all people receiving antiretroviral therapy will have viral suppression.[9] South Africa is currently some way from achieving this at 90, 61, and 47% respectively[1].

This study aid in understanding the factors contributing to switching the Tenofovir-backboned/Efavirenz-based first line ART that is currently being used in South Africa. By gaining knowledge on the timing of switching and the reason(s) for such a switch, it contributed understanding on the reason towards the non-achievement of the third 90 in South Africa, the study provided baseline data for future comparison with any new fixed-dose formulations, including Tenofovir-Lamivudine-Dolutegravir, which has become the preferred first line regimen in the Public Health Sector in South Africa.

Study Aim

The aim of this study is to assess side-effect profile of TDF-FTC-EFV fixed-dose-combination (TEE) by determining the event rate of switching away from the regimen and the reason for such switch in the setup of a Primary Health Care Clinic.

Objectives

Main objective: To determine the event rate of switching of the of TDF-FTC-EFV fixed-dose-combination over a period of 5 years.

Secondary objectives:

1) To describe the reasons of switching TDF-FTC-EFV fixed-dose-combination.

2) To determine the number (percent) of viral suppression and retention in care with satisfactory clinical outcome.

Methods

Study population and setting

The study is carried out at the Hannan Crusaid Treatment Centre (HCTC) in Gugulethu, Cape Town. This is a dedicated primary health care clinic linked to Gugulethu Community Health Centre that has been providing ART to HIV infected adults and children since 2002. The clinic is fully funded by Western Cape Provincial Government and has screened over 16000 HIV positive individuals since inception. In January 2019, over 7000 adults remained in care and on ART. The clinic supports a largely low-income community of approximately 100,000 people, with an HIV-seroprevalence of 13% in 2018 [10].

Study design

This is a retrospective analysis involving the review of the records of HIV infected adults receiving the fixed dose combination (TDF-FTC-EFV) antiretroviral therapy. These records are kept and password-protected electronically in the form of Microsoft Access database (Gugulethu ARV Register). The cohort is defined as ART-naïve adults starting the regimen between 1st September 2014 and 31st August 2019. Eligible study participants include HIV positive adults 18 years and older. The entire population started ART during the above defined time are included, hence no sample size estimation needed or performed.

Inclusion criteria:

- ART naïve patients, age 18 years and above, commenced on TEE ART between the 1st September 2014 and 31st August 2019.

Exclusion criteria:

- Pregnant at time of ART initiation
- Previously exposed to ART

The decision to exclude pregnant patients was that pregnancy follows a different ARV guideline (i.e. time interval of viral load testing, timing of second-line ART etc.). Patient with previous exposure to ART were excluded to minimize first-line ART resistance.

Study measurements and procedures

Data collection was done in 2 phases. Firstly study data was extracted from the Gugulethu ARV Register Database. Any missing data, such as reason for drug switch, was collected from the clinic's medical records by folder review. Study data collected were saved electronically into a Microsoft Excel sheet-based data-collection form.

Variables collected included:

i) Demographic variables such as age and sex, folder number.
ii) Laboratory variables such as baseline CD4 counts and HIV viral load.
iii) Treatment variables such as treatment start and stop date, reasons for drug substitutions, new replacement ART drug or regimens, outcomes (as defined below) and date of outcomes.

Clinical definitions

Primary outcome variable is defined as event rate of first drug substitution and time to event, such as drug-change, transfer-out, loss-to-follow-up or deaths.

Secondary outcomes include determining reason (i.e. adverse drug reactions or virological failure) for drug change and treatment effectiveness, determined by virological suppression and safety of the regime. Virological suppression is defined as having valid viral load (latest plasma HIV viral load within 12-months prior the event of drug-switch, transfer-out, loss-to-follow-up, death or censor date) less than 400 copies/ml. End-outcomes are categorized into remain in care (RIC), transfer out (TFO), loss to follow up (LTFU) and death. RIC are defined as study population remained in facility's care at censor date, whereas TFO are study population that are voluntarily transferred out to another facility's care prior censor date. RIC and TFO are used as proxy for good outcome, whereas death and LTFO loss to follow up are used as proxy for poor outcome. LTFU is defined as more than 28 days after medication-collection due date.

Analysis and Statistics

Data analysis was conducted by using STATA (version 11). Continuous variables are described using means and standard deviations for normally distributed data and medians and interquartile ranges for variables with a skew distribution. Categorical variables are described using percentages.

Kaplan-Meier analysis were used to measure time to first drug substitution. Kaplan-Meier analysis was chosen to measure the fraction of patients tolerating ARTs and/or with viral suppression for a certain amount of time after treatment.

Ethics statements

This study has received approvals from University of Cape Town (UCT)'s Human Research Ethics Committee (HREC, Ref: 525/2019) and from the Metro Health District Services of Western Cape Government as part of quality improvement.

This study is part of a bigger study from the Gugulethu ARV Register Database from Desmond Tutu HIV Foundation (DTHF) which received Ethics approval (HREC Reference number: 359/2002) to prospectively collect and maintain clinical data of patients of Hannan Crusaid Treatment Centre. Data sharing agreement between the investigators and DTHF was approved.

Folder number as an identifiable information was recorded for the purpose of folder review. It has been removed from the dataset prior statistical analysis and would not be attainable to parties other than the primary investigators.

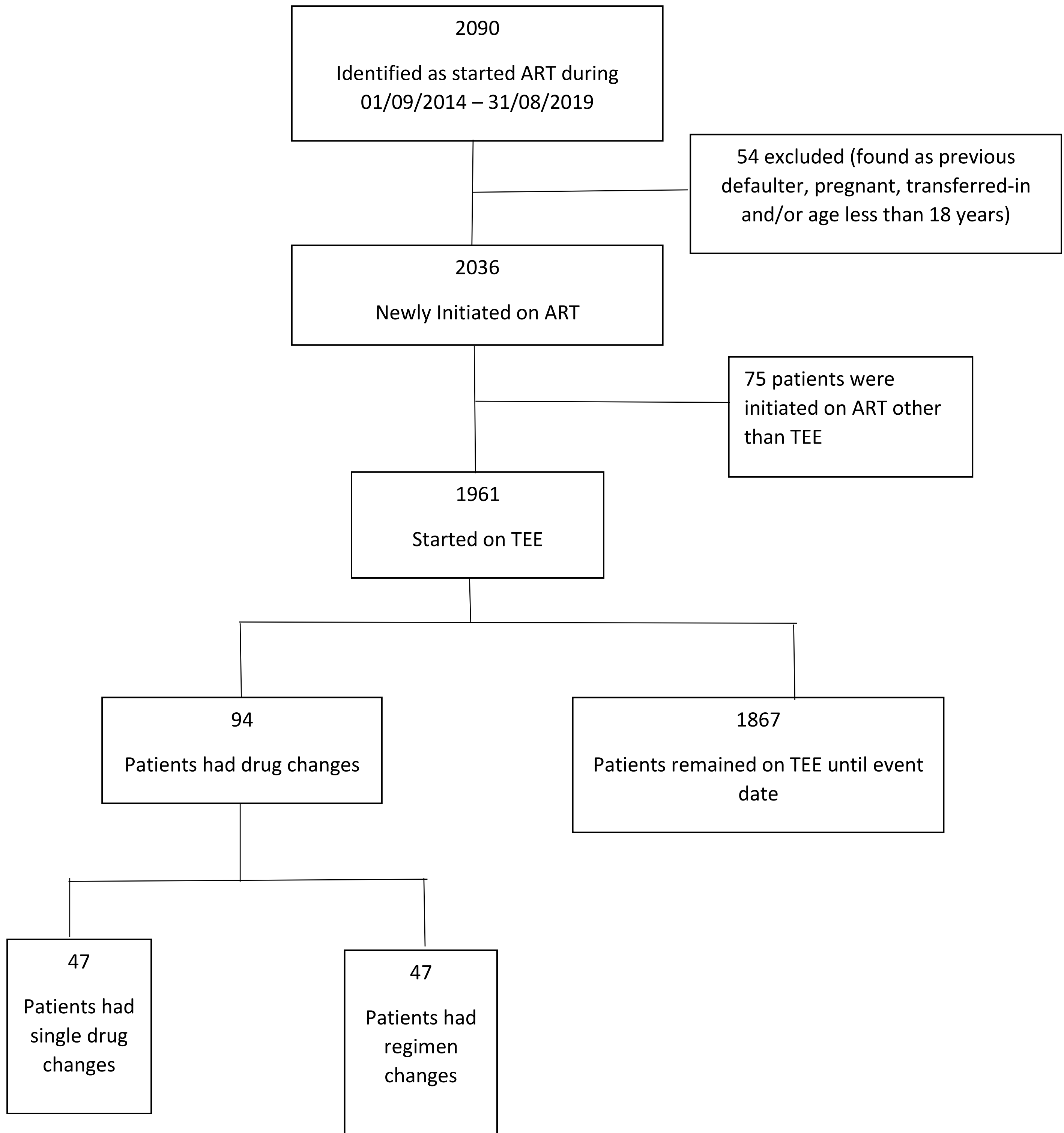
In the event of significant medical error noticed during the folder review, remedial action was taken to ensure patient safety.

Results

A total of 2090 patients were identified from the registry who had been started on ART for the first time between 1st September 2014 and 31st August 2019. 54 patients were found either to be previous defaulters, age less than 18 years, pregnant and were excluded. The remaining 2036 were newly started on ART.

Of the 1961 patients started on TEE ART. Ninety-four of the 1961 (4.8%) patients had drug substitution before the censor date, and the remaining 1867 (95.2%) patients remained on the TEE regimen until relevant event date. (Figure 1)

Figure 1. Description of patients starting ART at a community-based ART service in Gugulethu, Cape Town between September 2014 and August 2019.



Demographic and Clinical Characteristics

The cohort consists of predominantly female gender (n=1304, 64,1%), with a median age of 35 years (IQR 29 -43). Overall, the median duration of TEE ART exposure was 2.4 years (IQR 1.3 – 3.7) , with median CD4 at baseline of 292 (IQR 154 – 427) cells/uL. Patients who later required drug substitutions generally started with lower baseline CD4 counts (baseline median CD4 count of 187cells/uL and 117cells/uL for single drug change and regimen change respectively) compared to the No-switch group (baseline median CD4 of 302 cells/uL).

The majority of patients (n=1731, 85%) were initiated on ART during early stages of the disease (WHO stage 1&2) (Table 1)

Table 1. Demographic and clinical characteristics of ART naıve adults (n = 1961) started on TEE ART in Hannan Crusaid Treatment Centre.

	All Patients (1961)	**Patients had single Drug substitution (47)**	**Patients had Regimen changes (47)**	**No Switches (1867)**
Age (years) - median [IQR]	34.6 (28.4 - 42.3)	42 (32.5 - 50)	37.5 (30.8 - 42.5)	35 (28 - 42)
Sex - Female: n (%)	1259 (64%)	27 (2,1%)	31 (2,4%)	1201 (92,1%)
WHO Stage				
Asymptomatic (stage 1&2): n (%)	1685 (85.9%)	31 (66.0)	40 (85.1)	1614 (86.4)
Symptomatic (stage 3&4): n (%)	276 (14.1%)	16 (34.0)	7 (14.9)	253 (13.6)
Median TEE ART duration (years)- median [IQR]	2.2 (1.1 - 3.6)	0.5 (0.3 - 1.5)	1. 0 (0.8 - 1.5)	2.5 (1.4 - 3.8)
Baseline CD4 count (cells/uL)- median [IQR]	293 (156 - 430)	187 (76.5 - 288)	117 (43 - 190)	302 (169 - 437)

IQR – Interquartile range

Outcomes and drug substitutions

Of the 1961 patients started on TEE ART, at censor date 90.6% (n=1776) remained in care, 0.7% (n=13) were transferred out, 5.6% (n=110) lost to follow up and 3.1% (n= 62) died while on treatment. Indicating a 91.3% good outcome (RIC & TFO) and 8.7% poor outcome (LTFU & Death). Of the group who had no drug substitution, 8.78% (n=164) had poor outcome and of the group who had drug substitutions, 8.5% (n=8) had poor outcomes. (Table 2).

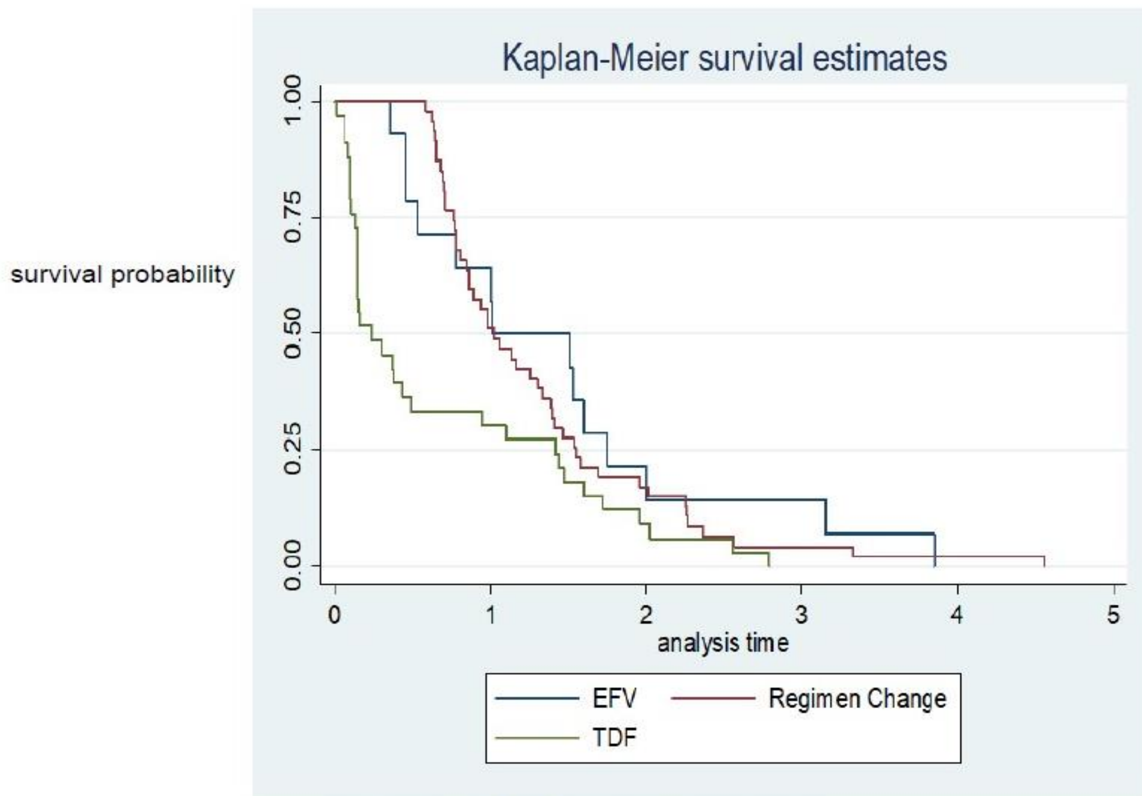
Table 2. Outcomes of various groups (n=1961)					
	RIC (n=1776)	TFO (n=13)	LTFU (n=110)	Deaths on Treatment(n=62)	Poor Outcome (LTFU&Deaths) %
No drug substitution	**1691**	**12**	**105**	**59**	*8.78%*
Total event of Drug Substitution	**85**	**1**	**5**	**3**	*8.5%*
Percentage of total	*90.6%*	*0.7%*	*5.6%*	*3.1%*	

RIC – Remain in care, TFO – transfer out, LTFU – loss to follow up

The cumulative exposure of TEE was 4520,77 person years and the median person-years of exposure to TEE was 2,4 person years.

Ninety-four (4.8%) of patients started on TEE first-line ART had their ART changed before censor date. The median (IQR) time to first drug substitution for TEE was 0.92 years (0.01 – 4.56). Of the 94 patients requiring drug changes, half (n=47) were single drug substitutions due to adverse drug effects or newly developed co-existing condition that contra-indicates the use of TEE regimen. The other half were due to virological failure.

On the Kaplan-Meier plot, TDF was associated with the higher risk of drug substitution over EFV. After 1 year of starting TEE regimen, the proportion of patients who had substituted TDF and EFV were 69,7% and 36% respectively, with the proportion of patients changing to second-line regimen 48,94%. The estimated median time to substitution for TDF and EFV were 0,24 year and 1,26 years respectively. Whereas the median time to change due to virological failure are 1,02 years. (Figure 2)



Numbers at Risk (number censored)

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
EFV	100(0)	64(5)	14(12)	14(12)	0(14)	
TDF	100(0)	30(23)	9(30)	0(33)		
Regimen Change	100(0)	51(23)	17(39)	4(45)	2(46)	0(47)

Figure 2. Kaplan-Meier estimates of time to first TDF, EFV drug substitution and drug change due to virological failure (analysis time in years).

At the end of 5 years, 86,23% of patients remained on TEE and remained in care.

Of the single drug substitution group (n=47), the majority were due to TDF (n=33, 70%), with reasons of tenofovir-induced renal toxicity (n=16, 48%, median time to change: 0.16 year), co-existing renal dysfunction (n=15, 45%), and concurrent usage of renal toxic drug Kanamycin (n=2, 6%), which precludes TDF usage.

Single drug substitutions due do EFV adverse effects consists of 14 patients (30%), with reasons of insomnia (n=2, 14%, median time to change: 1.18 years), neuropsychiatric adverse effects (n=3, 21%, median time to change: 1.6 years), gynaecomastia (n=2, 14%, median time to change 0.73 year), co-existing neuropsychiatric conditions (n=4, 29%, median time to change 0.89 year), and concurrent use of anti-multi-drug resistance TB drug Badaquiline (n=3, 21%), which precludes EFV usage.

Viral Load Suppression

On patients receiving TEE regimen (n=1961). At event date, valid HIV viral load (VL) results were obtained in 66.04% (n=1295) of patients with 90,58% (n=1173) viral load suppression. However, 29,88% (n=586) of patients does not have a valid viral load, resulting the proportion of viral load suppression of all patients entered care as 59,82%. (Table 3.)

Table 3. HIV Viral Load Outcome

	Total	No Drug Change				Drug-Change	
		RIC	T/O	LTFU	Died	Single switch	Regimen switch
Number: n(%)	1961	1691 (86,23%)	12 (0,61%)	105 (5,35%)	59 (3,01%)	47	47
Valid VL* result available: n(%)	1295 (66,04%)	1133 (67)	6 (50%)	56 (53,33%)	29 (49,15%)	24 (51.06%)	47 (100)
VL result not found: n(%)	3 (0.15%)	3 (0.18)					
Valid VL result unavailable: n(%)	586 (29,88%)	555 (32,82%)	1 (8,33%)	11 (10,48%)	15 (25,42%)	4 (8,51%)	
Event occurred before VL required: n(%)	77 (3,93%)		5 (41,67%)	38 (36,19%)	15 (25,42%)	19 (40,43%)	
Proportion suppressed of VL completed	1173 (90,58%)	1075 (94,88%)	6 (100%)	48 (85,71%)	23 (79,31%)	*21 (87.5%)*	
Proportion suppressed of all entering care	**59,82%**	63,57%	50%	45,71%	38,98%	44,68%	

VL – Viral load, RIC – Remain in care, TFO – transfer out, LTFU – loss to follow up

**Valid VL defined as VL performed within 12 months prior event date*

Of the subgroup of patients who has single drug substitutions, 91,67% of the TDF-group and 83,33% of the EFV-group has suppressed viral loads before the relevant drug substitutions. (Table 4.)

Table 4. HIV Viral Load outcome of Patients with Single-Drug Switch

	Tenofovir (n=33)	Efavirenz (n=14)
Valid VL result available: n (%)	12 (36,36%)	12 (85,71%)
Proportion suppressed of VL completed: n (%)	*11 (91,67%)*	10 (83,33%)
Valid VL result unavailable: n (%)	4 (12,12%)	
Event occurred before VL required: n (%)	17 (51,51%)	2 (14,29%)

Discussion

We observed that most of the patients remained in care and remained on TEE with large proportion of good treatment outcome (defined as remain-in-care and transfer-outs), demonstrating good drug tolerability of the combination-regimen. The percentage of poor outcome (LTFU and deaths) occurred in the no-drug change group does not differ significantly with the drug-change group, indicating that the event of drug-change, either single drug change or complete regimen change, does not contribute to poor treatment outcome.

The switch rate of 4.8% for TEE ART users over a period of 5 years is unexpectedly low. Estimated figures from previous studies which showed a TEE regimen-discontinuation rate ranges of 7% to 11% (Discontinuation rate of 10% due to adverse events were found in the TDF-FTC-EFV treatment arm in the SINGLE study[8]; 11% of background NNRTI resistance were found amongst the HIV population prior ART exposure according to the 2017/18 National Institute for Communicable Diseases Annual Review[11], and previous study on the same institution found a Tenofovir drug substitution rate of 7.7% [3]). The unexpectedly low substitution rate of TEE regimen may be explained by the reasonably good proportion of no-drug-change retention in care (86%, Table 5) with a good viral load suppression (94,88%) amongst this group, if they have their viral load tested. This suggests good adherence to medication and follow up appointments directly results in viral suppression. However, a large proportion (29,88% in the "Total" group and 32,82% in the "RIC" group) did not have their viral loads tested as per standard of care. This proportion of patient group leaves potential room for undetected or unreported LTFU, deaths and treatment failures, which may reflect into a higher switch rate.

The low EFV-substitution rate may due to inadequate mental health screening performed by the health care providers, since despite a high prevalence of depression amongst HIV positive patients on ART (21% positive depression screen demonstrated on a previous study done on the same study population[13]).

Kaplan-Meier estimates of time to first drug substitution (Figure 2), showed that most of the TDF substitution events occurred during the first six months of starting TEE regimen. EFV substitutions and regimen change occurred within first two years. The total number of drug substitutions due to EFV and virological failure constitutes of 64,89% of total switches. With the new fixed-dose combination ART in which Efavirenz is replaced by Dolutegravir, the drug substitution risk of EFV and virological failure of TEE might be mitigated since dolutegravir is better tolerated and more genetically robust against viral resistance. However, adverse effects of Tenofovir will persist and early monitoring (esp. renal function) is still required.

A high proportion of those who had a viral load drawn achieved viral load suppression (90,58% in the "Total" and 94,88% in the "RIC" group). This might not be representative of the true viral load suppression in the cohort that entered care during the study period, as nearly a third (29,88% and 32,82% in "Total" and "RIC" group respectively) did not have valid viral load test performed as per standard of care. Potential reasons may include substandard care delivered by treating clinicians, undocumented programme losses such as LTFU, deaths, and patient factors such as poor adherence to medication and routine follow up. Overall, the proportion of viral load suppression of those who commenced TEE ART became 59,82% ("Total" group) and 63,57% ("RIC" group). This is slightly higher than the national data of 47%, but far below the 90-90-90 target of 90% virological suppression. Urgent further study to ascertain the major reasons for this, and to suggest quality improvements is required.

While symptomatic adverse drug effects may result a lower viral load suppression (Table 6), indicating another benefit for the better tolerated dolutegravir-based regimen.

Limitations

The source data registry was not designed specifically to answer the aim and objective of this study, resulting extra time needed to gather the additional data that is not recorded in the original registry.

The analysis is restricted to time to first drug substitution only, any subsequent drug substitution after the first event are not examined, thereby underestimating the true number and reason for overall drug changes. Nonetheless, this study is based on robust data set, with a large sample size, long follow-up period and minimal missing data in the variables.

Implications for future research

Further study may be needed to determine the prevalence of long term adverse mental health effects for patients on EFV. (We await the results from CONNECT, which looks at neurocognitive function, mental health symptoms and cerebral spinal fluid analysis of patients before and after Efavirenz substitution with Dolutegravir).

Further study by means of clinical audit is needed to determine the reason(s) for the absence of valid viral load tests. As the later contributed a third of the population cohort and cause an impact on the successfulness of target against virological suppression.

Conclusion

Better programmes are required to enrol people living with HIV to care at early phases of their disease and improved systems for viral load monitoring, mental health screening and patient tracing are required for those in care.

Tenofovir-Emtricitabine-Efavirenz combination treatment, provided that treatment is started early and adequate adherence to care is maintained, remains an excellent first-line ART option for people living with HIV. With the new Tenofovir-Lamivudine-Dolutegravir combination regimen as the now preferred first-line ART in South Africa, despite higher barrier to resistance and anticipated lower neurocognitive side-effects, clinicians should still remain cognisant of the adverse drug effects of Tenofovir.

Declaration of Conflict

The investigators declare no conflict of interest.

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