

Prevalence of unsuppressed viraemia in HIV positive female sex workers on the daily single dose TDF/3TC/EFV tablet for 6 months: PSI-Zimbabwe sex worker cohort

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Mini-thesis presented for the Masters degree in Clinical Epidemiology in the Faculty of Medicine and Health Sciences, at Stellenbosch University

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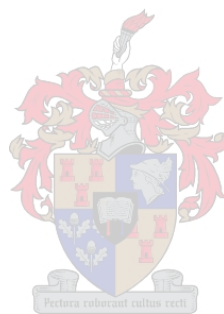


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Declaration

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Abstract (246 words)

Background: Data on viral suppression and adherence patterns of anti-retroviral therapy (ART) naïve HIV positive female sex workers (FSWs) initiated on the Tenofovir/lamivudine/Efavirenz (TDF/3TC/EFV) fixed dose combination are scarce in Zimbabwe. The objectives of this study were to describe the prevalence of and factors associated with unsuppressed viraemia as well as the mean adherence of FSWs on the Efavirenz based fixed dose tablet after 6 months of treatment.

Methods: A retrospective record review was done on 77 FSWs who had been initiated on TDF/3TC/EFV and had a 6 months post initiation viral load test result at 2 FSW clinics in Gwanda and Bulawayo, Zimbabwe. Recruitment into the clinics was done between July 2013 and September 2015. Data on monthly adherence per pill count, 6 months viral load test result and possible predictors of unsuppressed viraemia were collected.

Results: Prevalence of unsuppressed viraemia after 6 months on TDF/3TC/EFV FDC tablet was 7.78% (95%CI, 1.67-13.92 %) while viral suppression occurred in 92.22% (95%CI 83.8-97.1%). Based on the 35 patients with complete adherence data, the mean adherence was 99.69% (95%CI, 99.48%-99.91%). All 35 had adherence >95% classified as good. Only comorbidity (Adjusted OR 23.31, 95%CI

1.74-310.65, $p = 0.017$) and baseline CD4 count (Adjusted OR 0.9886; 95%CI 0.9774-0.9998, $p= 0.047$) showed independent associations with unsuppressed viraemia.

Conclusion: In the first 6 months on TDF/3TC/EFV, ART there is a low prevalence of unsuppressed viraemia, high viral suppression rates and high adherence rates in naïve HIV positive FSWs in our setting.

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List of abbreviations

- ART – Anti-Retroviral Therapy
- EFV- Efavirenz
- FDC- Fixed dose combination
- FSWs- Female sex workers

- HIV – Human Immuno-deficiency Virus

- PCR – Polymerase Chain Reaction

- PSI – Population Services International

- OR – Odds Ratio

- RNA – Ribonucleic Acid

- TDF- Tenofovir

- WHO – World Health Organization

- 3TC – Lamivudine

- 95% CI – 95% Confidence Interval

Key Words

Female sex workers, fixed dose combination, anti-retroviral therapy, HIV, adherence, viral load, Zimbabwe

Background

According to WHO, the global prevalence and incidence of HIV is generally declining but remains disproportionately high in some population sub-groups termed 'key populations' in view of their behaviour related increased risk¹. These include sex workers, prisoners, intravenous injection drug users, men who have sex with men and the transgender community¹. Prevalence in these groups still resembles the high rates found at the inception of the epidemic before major roll outs of treatment and prevention programs. This suggests that these special groups have generally not received enough attention in such programs. In Zimbabwe the estimated HIV prevalence in sex workers is between 50 and 70% compared to 15% in the general population². Of all new HIV infections worldwide, between 40 to 50% are occurring in key populations³. It is from such observations that the WHO recognised that if the goal of epidemic control by 2030 is to be attained; key populations need to be addressed³.

Evidence points out to reduction in HIV transmission in sex workers and their clients with focused, targeted interventions that include treatment with highly active antiretroviral drugs (HAART) commonly known as treatment for prevention^{2,4, 5}. This evidence, recognition by international key stakeholders and the recent WHO Guidelines has resulted in a huge global scale up of HIV prevention and treatment interventions in sex workers. WHO recommends that HIV positive sex workers receive the same antiretroviral therapy management as the general population¹. It is also recommended that the single tablet per day fixed dose combination (FDC) of Tenofovir, Lamivudine and Efavirenz (TDF/3TC/EFV) be used as it reduces pill burden and improves adherence¹. The current guidelines and practice are based on evidence from the general population, and the assumption that the improved adherence that results from the Efavirenz based FDC's reduction in pill burden will do the same in FSWs. This may not necessarily be true given fundamental differences that may exist between the general population and female sex workers (FSW) e.g. sleep/work times that make generalizability questionable.

The study sought to interrogate the FDC use in FSWs by answering the initial key questions surrounding viral suppression and adherence in this key population group.

Key pre-antiretroviral therapy counselling messages include use before sleep for better tolerance of side effects ¹. While it is known that Efavirenz causes neuropsychiatric side effects including confusion, sleep disturbances, dizziness and vivid dreams, it was not known whether these were a barrier to adherence in sex workers ⁶. In fact there is a general lack of data on FSWs adherence patterns while a lack of access to healthcare could be a significant barrier in HIV control efforts in this key population group ^{7,8}. Our study was in response to calls for researchers to investigate issues around adherence in key populations⁹. The purpose of this study was to describe the prevalence of and factors associated with unsuppressed viraemia in FSWs on the Efavirenz based fixed dose combination pill after 6 months of treatment. Since there have been concerns about poor adherence in sex workers particularly those that use recreational drugs, we also sought to describe their adherence to the FDC ¹⁰. Poor adherence to treatment could lead to unsuppressed viraemia, virologic treatment failure and hence high infectivity as well as the risk of spreading drug resistant strains of the HIV virus. Drug resistance against a background of high baseline prevalence in this key population group could be disastrous if the high prevalence translates to high prevalence of resistant strain. This would be of significant public health concern since second line antiretroviral drugs are very expensive and the cost of managing morbidity in people with resistant virus would be much higher. We explored possible predictors to unsuppressed viraemia in this group including poor adherence, baseline characteristics, report of neuropsychiatric side effects and alcohol/substance abuse.

Research Question

What are the prevalence and predictors of unsuppressed viraemia after 6 months of treatment on the Efavirenz based fixed dose combination Antiretroviral Therapy in HIV positive adult female sex workers in the PSI-Zimbabwe cohort?

Aims and Objectives

The aim of the study was to improve understanding of the burden of unsuppressed viraemia and its predictors in early EFV based FDC antiretroviral treatment of female sex workers. The primary objective was to estimate the prevalence of unsuppressed viraemia in HIV positive female sex workers on Tenofovir/lamivudine/Efavirenz

(TDF/3TC/EFV) single tablet a day fixed dose combination after 6 months of treatment. Secondary objectives were to describe the mean adherence of the Population Services International (PSI)-Zimbabwe sex worker cohort over 6 months and to determine factors associated with poor viral suppression in sex workers on the tablet.

Methods

Study Design

We conducted a retrospective record review of routine adherence data recorded monthly and HIV viral load results measured at 6 months after initiation of the EFV based FDC. The study was conducted at PSI-Zimbabwe sex worker clinics in the Zimbabwean towns of Gwanda and Bulawayo. The participants had been enrolled on to the clinics' Anti-Retroviral Therapy program from July 2013 for the Bulawayo clinic and July 2014 for the Gwanda clinic up to September 2015. Data collection was done from 22/10/2015 to 06/11/2015.

Study Population and Sampling

The target population was HIV positive female sex workers in Gwanda and Bulawayo. The target population is hard to reach, specific and limited in availability hence we preferred a record review. Attendees to the sex worker clinics were assumed to be representative of the HIV positive sex worker population in Zimbabwean towns and presenting in random order. Recruitment into the ART program at the clinic was open to all FSW of all ages. Most would have come as walk-ins mobilised at hot spots such as brothels and night clubs while some came as referrals from partner organizations dealing with FSWs. All HIV positive treatment naïve FSWs over the age of 18 years being initiated on the FDC tablet at the clinics with a 6 months post initiation HIV viral load result were eligible. 176 were potentially eligible by virtue of being on the FDC for more than 6 months and all had an HIV viral load blood sample taken since this is routine. However, 99 did not have an HIV viral load result by the end of data collection due to huge backlogs with the laboratory. As such, a total of 77 records, 18 from Gwanda and 59 from Bulawayo clinics were found to be eligible (see figure 1).

Measurements

The HIV viral load results and adherence data were obtained as routine data from EpocWeb, an electronic patient file management system used at the clinics. Patient HIV viral loads were measured routinely at 6 months of treatment at Newlands clinic laboratory in Harare using HIV RNA PCR based COBAS Ampliprep/Taqman 48. Replicates for HIV negative, low positive and high positive controls were included in each batch for quality assurance. Percentage adherence were calculated by nurses using pill counts against dispensed number of tablets monthly and imputed onto EpocWeb. Where complete data were available, the mean adherence for each patient was calculated as the average monthly adherence for the 6 months. Reports of neuropsychiatric illness, comorbidities and opportunistic infection were obtained on the diagnoses section while that of alcohol use and recreational drug use were found on the history section.

Data Management

Data collected

Data collected included HIV viral load, classified as suppressed when it is less than 1000 copies per ml, and monthly percentage adherence which was documented on visits in the patient electronic record. The calculated 6 months mean adherence was classified as good when greater than or equal to 95% or poor when less than 95%. Other data collected include age, clinical stage at ART initiation, baseline CD4 count, presence of incomplete 6 months adherence data, report on adverse events during treatment, presence of co-morbidities, occurrence of opportunistic infections, alcohol use status (alcoholic/non-alcoholic) and recreational drug use.

Data Collection Procedures

Data were collected retrospectively directly from queries run on Epoc Web and manually captured onto the patient's data collection form identified only by a unique study ID with no meaning external to the study. The data collected on the forms was then electronically captured into an Excel spread sheet data extraction form.

See Appendix A for the data capture form and coding used.

Statistical Analysis

This study had 2 components. The descriptive component aimed to assess the extent of the burden of unsuppressed viraemia and the mean adherence in FSWs.

The analytical component aimed to identify risk factors for poor virological suppression in FSWs. In determining the sample size, the study aimed to estimate the prevalence of unsuppressed viraemia with a precision of +/- 5%. Some studies have estimated the prevalence at between 5-15% in the general population ¹¹. We expected it to be around 10% in our cohort. Allowing for 10% missing data the required sample size was calculated at 153 participants. Only 77 meeting inclusion criteria due to time constraints were identified, which resulted in only a small loss of precision. Statistical analysis was done using Stata version 13 ¹². The prevalence of unsuppressed viraemia was calculated as a proportion with a 95% confidence interval and the mean adherence was calculated as a percentage with its standard deviation, and 95% confidence interval.

Associations between categorical risk factors (clinical stage, incomplete adherence data, neuro-psychiatric side effects, and presence of co-morbidity, opportunistic infections, alcohol use and recreational drug use) and the outcome of unsuppressed viraemia were assessed using Pearson's chi square tests. Wilcoxon rank-sum test was used to compare mean adherence, age, and baseline CD4 count between the participants with and without suppression. Factors and covariates identified as associated with unsuppressed viraemia at the 0.1 level of significance on univariate analysis were entered as independent variables in a binary logistic regression analysis in order to ascertain odds ratios and 95% confidence intervals for independent risk factors for the outcome. The final model was arrived at using backward elimination with entry and exit probabilities set at 0.1 and 0.05 respectively.

Results

Characteristics of participants

Table 1 shows the demographic and clinical characteristics for the participants included in the study. A total of 77 patients who were anti-retroviral therapy (ART) naïve, then initiated and kept on the Tenofovir/lamivudine/Efavirenz fixed dose combination tablet and had an HIV viral load result at 6 months on treatment's records were reviewed. 18 were from Gwanda and 59 were from the Bulawayo clinic. Figure 1 shows the flowchart for enrolment with details of the potentially eligible to the final total used for analysis after application of the eligibility criteria. The median

age was 31 (IQR, 26-35) years. At ART initiation the median CD4 was 282 (IQR, 153-348) cells/dl. Of the 75 who had WHO clinical staging data 47.37% were stage 1, 22.37% were stage 2, 23.68% were 3 and 6.58% were stage 4. Only 35 patients had complete adherence data. Of these, all had good 6 months mean adherence above 95% per pill count. None of the 77 patients had evidence of reporting neuropsychiatric side effects of Efavirenz in the records. Thirteen (16.88%) had comorbidities of which 5 (38.46%) had Iron deficiency anaemia, 6 (46.15%) had anaemia of chronic illness and 2 (15.38%) had hypertension. 4 out of the 6 (66.67%) unsuppressed clients had an anaemia of chronic illness diagnosis, 1 had Iron deficiency anaemia while 1 had no comorbidity. Nine (11.69%) were diagnosed with opportunistic infections of which 7 (77.78%) had oral candidiasis while 2 (22.22%) had oesophageal candidiasis. Data on alcohol and recreational drug use was found in only 20 records of which 12 (60%) reported alcohol use, and none reported recreational drug use.

Prevalence of unsuppressed viraemia

All participants in the study had an HIV viral load result recorded after 6 months of treatment. The prevalence of unsuppressed viraemia after 6 months on TDF/3TC/EFV FDC tablet was 7.78% (95%CI, 1.67-13.92 %). Viral suppression rate in this sex worker population was estimated at 92.22% (95%CI, 86.08-98.33%).

Table 1: Demographic and clinical characteristics (N =77)

Characteristic	Result
Age (median, IQR) years	31 (26,35)
*Mean Adherence (median, IQR) %	99.7 (99.5-99.9)

Baseline CD4 count (Median, IQR) cells/dl		282 (153-348)
*Adherence, no. (% with complete data)	Good	35 (100)
	Poor	0
HIV viral load, no. %	Suppressed <1000c/ml	71 (92.22)
	Unsuppressed >1000c/ml	6 (7.78)
Opportunistic infections no. % Total 9 (11.69)	Oral candidiasis	7 (9.09)
	Oesophageal candidiasis	2 (2.6)
Comorbidity, no. % Total 13 (16.88)	Iron deficiency anaemia	5 (6.49)
	Anaemia of chronic illness	6 (7.79)
	Hypertension	2 (2.6)
‡Alcohol, no. (% with complete data)	Users	12(60)
	Non-users	8 (40)

*incomplete data, only 35 participants out of 77 had complete 6 months adherence data

‡ Only 20 participants had documented data on alcohol intake

Not recorded for recreational drug use

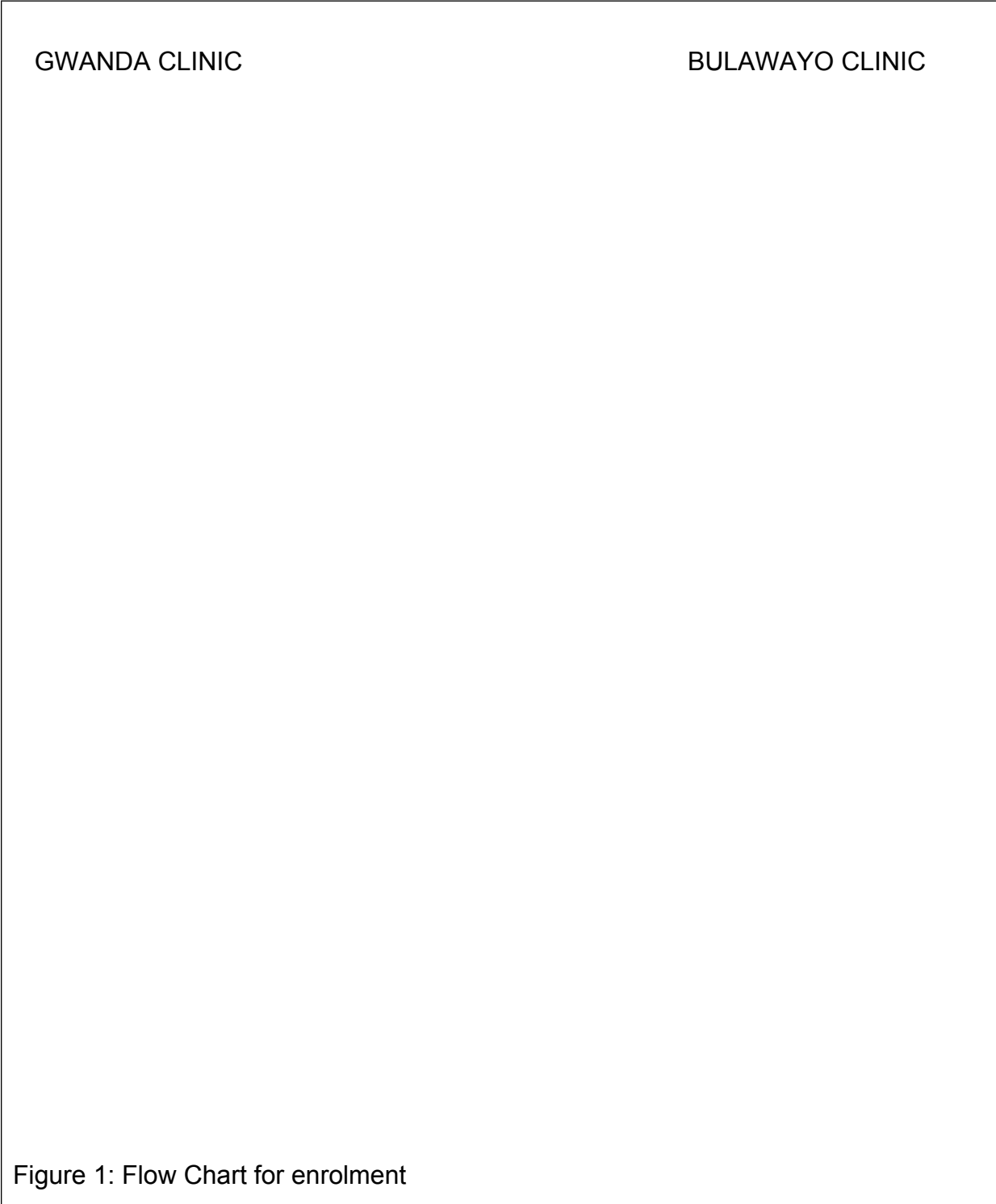


Figure 1: Flow Chart for enrolment

Mean adherence

For the first 6 months after ART initiation, based on the 35 patients with complete adherence data the mean adherence was 99.69% (95%CI, 99.48%-99.91%). All 35 had adherence >95% classified as good per pill count. 42 patients (54.55%) had incomplete 6 months adherence data.

Factors associated with unsuppressed viraemia in female sex workers

On univariate analysis, baseline CD4 count showed a statistically significant association with unsuppressed viraemia (OR 0.989, 95%CI 0.977-0.9998, $p=0.001$) while age and mean adherence were not associated (see Table 2). Incomplete 6 months adherence data, neuropsychiatric side effects, type of comorbidity, alcohol use and recreational drug did not show any statistically significant association with unsuppressed viraemia. Presence of an opportunistic infection showed a weak association with a p -value of 0.086 while presence of a comorbidity ($p<0.001$) showed strong association with unsuppressed viraemia. Clinical stage ($p=0.001$) showed a statistically significant association and more advanced disease (stage 3&4) showing an even stronger association with a $p<0.001$. Clinical stage could not be included in the logistic regression analysis due to 100% of the unsuppressed patients being in stage 3 or 4.

Further analysis with logistic regression modeling was done on baseline CD4 count, presence of co-morbidity and presence of an opportunistic infection (see table 3). Presence of a comorbidity had a statistically significant association with an adjusted OR of 23.308 (95%CI, 1.75-310.65, $p=0.017$). Baseline CD4 count had a weak association with an adjusted odds ratio (OR) of 0.989 (95%CI, 0.9774-0.9998). There was a non-statistically significant association between the presence of opportunistic infection and unsuppressed viraemia, with the adjusted OR 4.34 (95%CI, 0.25-73.98, $p=0.310$).

Table 2: Factors tested for association with unsuppressed viraemia- univariate associations

Variable	Overall Result	Suppressed	Unsuppressed	OR (95% CI)	P value
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Age, <i>Median (IQR)</i> years	31 (26,36)	31 (26,35)	34.5 (22,39)		0.607
Baseline CD4, <i>Median (IQR)</i> cells/ml	282 (153,348)	289(187,350)	51.5 (21,100)	0.984 (0.973-0.996)	0.007
Mean adherence, <i>mean (95%CI)</i> %	99.7 (99.5-99.9)	99.64 (99.5,100)	100 (100,100)		0.167
Incomplete adherence data, <i>number (%)</i>	42 (54.55)	41 (57.75)	1 (16.67)	0.146 (0.163-1.318)	0.087
Advanced Clinical stage 3&4, <i>number (%)</i>	23 (30.26)	17 (24.29)	6 (100)		<0.001
Comorbidity, <i>number (%)</i>	13 (16.88)	8 (11.27)	5 (83.33)	39.375 (4.070-380.959)	<0.001
Comorbidity type				1.108 (0.223-5.498)	0.9
Iron deficiency anemia	5	4 (5.63)	1 (16.67)		
Anemia of chronic illness	6	2 (2.82)	4 (66.67)		
Hypertension	2	2 (2.82)			
Opportunistic infections, <i>number (%)</i>	9 (11.69)	7 (9.86)	2 (33.33)	4.570 (0.710-29.610)	0.086
Neuropsychiatric side effects	0	0	0		
Alcohol use, <i>number (%)</i>	12 (60)	11 (57.89)	1 (100)		0.402
Recreational drug use	0	0	0		

Table 3: Final multivariate logistic regression model

Factor	Adjusted OR (95% CI)	P-value
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Comorbidity	23.308 (1.749-310.646)	0.017
Baseline CD4	0.9886 (0.9774-0.9998)	0.047

Discussion

Our study estimated the prevalence of unsuppressed viraemia in the PSI-Zimbabwe FSW cohort on the FDC TDF/3TC/EFV tablet to be 7.78% after the first 6 months of treatment. Most of the participants, 92.22%, had viral suppression, a figure that is above the WHO targets of having at-least 90% of all clients on ART suppressed by 2020. These estimates are above those given in other studies for anti-retroviral therapy in general. A study in Burundi reported that 81.8% of FSWs had undetectable viral load results ¹³. A recent systematic review that included studies from 21 different sex worker populations in Africa, Asia, South and Central America and the Caribbean gave pooled estimates of 57% (95% CI:46-68%) achieving viral suppression ¹⁴. All the 35 participants with complete adherence data had good adherence measured as >95% adherence per pill count. The mean adherence was very high at 99.69%. These figures are biased upwards since non-compliant patients are more likely not to have complete adherence data; however the impact of this bias is minimal given that the more objective measure of HIV viral load showed high suppression rates. Furthermore, of those with good adherence, 14% (5/35) were unsuppressed, compared with the 7.8% of the total cohort. Thus it appears that the possible bias was minimal. Our study is the first to give such data on the sex worker population on an Efavirenz based regimen in Zimbabwe. Our estimates are higher than the 55.5% observed in a Canadian study where concerns were raised about suboptimal adherence (on ART in general) in the sex worker population ¹⁰. The low prevalence of unsuppressed viraemia, and high adherence levels should encourage clinicians to scale up TDF/3TC/EFV roll out in FSW populations in Zimbabwe and similar settings. No neuropsychiatric side effects of efavirenz were reported in this study. An advanced clinical stage (3 & 4), low baseline CD4 count and the presence of a comorbid condition were all independently associated with unsuppressed viraemia. Larger studies in similar settings may be considered to

investigate other predictors and to explore further those studied (but may have had small differences missed due the small sized nature of our study). Since high adherence levels were observed even in those that were unsuppressed, concerns for transmitted resistance need to be raised ¹⁵. As such, patients with these independent predictors may be considered for HIV resistance testing before ART initiation. They would then be initiated on sensitive drugs to minimize the risk of the virus acquiring more mutations and developing resistance to multiple drugs. Further studies to determine the utility of drug sensitivity testing in FSWs with these predictors in resource poor settings such as the one in which our study was carried out need to be done.

The study had limitations that need to be considered in the interpretation of findings. The study sample was small, reducing the power and hence the ability to detect small differences in the variables. Though there were many FSWs who could have been on TDF/3TC/EFV for more than 6 months, not many had a 6 months HIV viral load result due to poor turnover, huge backlogs and delays in processing specimens at the out-sourced laboratory. Bias may have been introduced as patients clinically or immunologically failing are more likely to have their viral load results followed up with the laboratory and hence more likely to be included in the study yet they are more likely unsuppressed. However the effect of their inclusion would have been to increase the prevalence of unsuppressed viraemia and decrease the viral suppression rates when in fact the study showed a low estimate for the prevalence and a high viral suppression rate thereby increasing the validity of the study estimates. There needs to be an increase in efforts to increase the turnover of viral load results in Zimbabwe.

The precision of our estimates was affected by the small sample size for the association of comorbidity and unsuppressed viraemia which had statistically significant odds ratio of 23.31 but a very wide confidence interval of 1.75 to 310.65. Prevalence of unsuppressed viraemia, mean adherence and baseline Cd4 counts estimates were reasonably precise. Since we used an observational study design, confounding could only be controlled for to an extent in the analysis of the data; hence findings need to be interpreted with caution as other unmeasured factors may have influenced the results. There was also a major challenge with missing data particularly for adherence, alcohol and recreational drug use. Using pill count as a

measure of adherence is easily prone to manipulation by the patient, the impact of this was however likely minimal since there was satisfactory viral suppression. Data on the prevalence of unsuppressed viraemia and factors associated with it in FSWs within the Zimbabwean context are scarce¹⁴. This study formed an important first step to addressing concerns such as the question of suitability of an Efavirenz based regimen in sex workers that may be a barrier holding back healthcare providers from scaling up treatment roll out. Our study suggests that it is suitable to use an EFV based regimen in sex workers with low prevalence of unsuppressed viraemia after 6 months of use. It also gave early insights into concerns about risk and burden of transmitted resistance in the sex worker population in Zimbabwe. The findings of our study will be of importance to government health departments, educational institutions and non-governmental institutions in formulating policies and coining interventions that are tailor made for this key population group, including the development of group specific messages.

Conclusion

In the first 6 months on TDF/3TC/EFV, ART naïve HIV positive FSWs showed a low prevalence of unsuppressed viraemia, and high adherence rates. Policy makers and clinicians should be encouraged to roll out this FDC pill to FSW. FSWs with advanced HIV disease, comorbidity and low baseline CD4 counts should be watched closely for poor viral suppression. Though further studies are needed, drug sensitivity testing could be considered before ART initiation in HIV positive FSWs with these possible predictors.

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Appendix 1: Data collection form

Date of data collection

PROJECT S15/07/144, Incidence of unsuppressed viraemia in HIV positive sex workers on the daily single dose TDF/3TC/EFV tablet for 6 months: PSI-Zimbabwe sex worker cohort

PART A

Study ID

Study Site Tick one box

1. Bulawayo

2. Chivhu

3. Gundu

4. Gwanda

5. Magunje

6. Kadoma

7. Kariba

Age

6 Months Viral Load *tick appropriate box*

<1000 Copies per ml (Suppressed)

>1000 Copies per ml (Unsuppressed)

Adherence

Month 1

Month 2

Month 3

Month 4

Month 5

Month 6

6 months Mean Adherence

Overall Adherence *tick appropriate*

Good Adherence

Poor Adherence

PART B

WHO Clinical Stage at ART initiation

Baseline CD4 Count

Report of Neuropsychiatric Side Effects *tick appropriate*

Yes

No

Nature of Neuropsychiatric Side Effects *tick appropriately*

Drowsiness

Insomnia

Nightmares/vivid dreams

Confusion

Memory loss

Hallucinations

Delusions

Depression

Other

Describe.....

Alcohol use

Yes No

Alcoholic by CAGE Score

Yes No

Inadequate information in records to classify

Recreational Drug Use

Yes No

Type of recreational drug used.....

Presence of Opportunistic Infections

Yes No

Type of Opportunistic infection.....

Co-morbidities

Yes No

Nature of Co-morbidity

Appendix 2: Ethics Clearance



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Request for Modifications New Application

11-Aug-2015
Moyo, Brian BK

Ethics Reference #: S15/07/144

Incidence of unsuppressed viraemia in HIV positive sex workers on the daily single dose TDF/3TC/EFV tablet for 6 Title: months: PSI-Zimbabwe sex worker cohort.

Dear Dr Brian Moyo,

The **New Application** received on **06-Jul-2015**, was reviewed by members of **Health Research Ethics Committee 2** via Expedited review procedures on **07-Aug-2015**.

In principle the Committee is in agreement with the project, but requested that you should attend to the following matters before the project could be finally approved. The following modification(s) and/or additional information about the research or the application are requested:

1. Our HREC can grant a waiver of informed consent on the condition that the data is completely anonymised i.e. even the investigators should not be able to link the study codes back to any patient. Kindly revise in the protocol and resubmit. Please also submit a copy of your data collection sheet for review.

On receipt of the additional information / corrected document(s) the application will be reconsidered.

Please provide a letter of response to all the points raised IN ADDITION to HIGHLIGHTING or using TRACK CHANGES function indicate ALL corrections / amendments of ALL DOCUMENTATION, clearly in order to allow rapid scrutiny and appraisal.

The HREC has determined that your response to this Request for Modifications may be reviewed via Expedited review procedures. Based on your response the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or refer your response to the convened HREC.

Please note that the application for approval and registration of this project would be cancelled automatically if no feedback is received from you within 6 (six) months of the date of this letter.

Please note that you **may not** recruit subjects until you receive a **written notice of HREC approval** that will include the date-stamped informed consent document(s) to use when seeking consent from subjects.

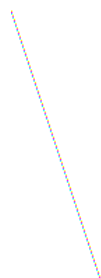
For standard HREC forms and documents please visit: www.sun.ac.za/rds

If you have any questions or need further assistance, please contact the HREC office at 219389207.

Sincerely,

Mertrude Davids
HREC Coordinator
Health Research Ethics Committee

Appendix 3: Ethics Amendments



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Ethics Letter

20-Oct-2015

Ethics Reference #: S15/07/144

Title: Incidence of unsuppressed viraemia in HIV positive sex workers on the daily single dose TDF/3TC/EFV tablet for 6 months: PSI-Zimbabwe sex worker cohort.

Dear Dr Brian Moyo,

The Health Research Ethics Committee approved the amended documentation:

Amendment #1, dated 29 September 2015 - substitution of a clinic for data collection purposes

If you have any queries or need further help, please contact the REC Office 219389819.

Sincerely,

REC Coordinator
Ashleen Fortuin

SAJID Author Guidelines

Manuscripts submitted to the SAJID must be in the form of *Research Articles, Brief Reports, Clinical Case Studies, Correspondence, Reviews, State-of-the-Art Articles, Commentaries and Opinion Papers, Editorials or Supplement Articles*. The Journal welcomes the publication of *Guidelines, Conference Proceedings Newsletters or Press Releases, and Book Reviews*. Articles, Brief reports and Reviews are peer reviewed; other categories are reviewed by the Editors. Commentaries and Editorials are generally invited contributions, indicating the authors' identity, while manuscripts in the form of Reviews, and State-of-the-Art Articles may also be requested by the Editors.

All manuscripts must have conflict of interest and funding statements. When authors submit a manuscript, whether an article or a letter, they are responsible for disclosing all financial and personal relationships that might bias their work. To prevent ambiguity, authors must state explicitly whether potential conflicts do or do not exist. Authors should do so in the manuscript on a conflict-of-interest notification page that follows the title page.

Manuscripts describing research in human subjects or animals must indicate ethics clearance from appropriate research review committees. When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

Articles describe original investigations at an acceptable degree of completion, constituting an advance in the field. Articles must not exceed 3500 words of text, without counting the abstract, references or legends, and illustrations and tables must be limited to the minimum necessary for clear and concise presentation. The abstract must either be structured, using *Background, Methods, Results, and Conclusions* as headings and comprising no more than 250 words, or unstructured with a 200 word limit. Articles are limited to a maximum of 7 insets (tables and figures combined) and 50 references.

Brief Reports present complete studies that are narrower in scope than those described in *Articles* or that present new developments. Manuscripts that are descriptive or primarily methodological in nature, or that describe *in vitro* chemotherapeutic studies should, in general, be submitted as *Brief Reports*. *Brief Reports* include an abstract (no more than 100 words) and are limited to a total of no more than 2000 words of text, a total of 2 inserts (tables or figures), and 15 references.

Correspondence (letters) must be submitted in reference to a previous publication in *SAJID* (within the previous 12 months), or relate to a topical matter in line with the interests of FIDSSA, PHASA or their affiliated societies. Please prepare the letter in manuscript format, including a title page. The letter must not exceed 750 words of text, 1 insert (table or figure) and 10 references.

Commentaries and Editorials are generally invited by the Editor and are overviews of articles in *SAJID*, or of other research in epidemiology or infectious diseases, or matters relating to public health and other issues of special interest to FIDSSA, PHASA or their associated societies. Unsolicited commentaries are also considered.

Reviews and State-of-the-Art Articles that are research oriented or fall within the fields of interests of FIDSSA, PHASA or any of their affiliated societies will be considered for publication by *SAJID*. Prospective authors of such manuscripts are advised to communicate with the Editor in advance to ensure that a specific

contribution is deemed appropriate and timely. Manuscripts of Reviews and State-of-the-Art Articles will be peer-reviewed.

Reviewers

The Journal would encourage authors to supply the names of at least 2 potential reviewers for their manuscript, as well as to indicate any reviewers they would feel may have a potential conflict of interest with regard to their submission.

Supplements

Requirements for supplement manuscripts generally follow those for SAJID manuscripts, including conflict of interest and funding statements. Inquiries relating to suitability of topic, programme organisation, production and costs should be made to the Editor.

Evaluation of manuscripts

Review procedure. The Editor-in-Chief and Emeritus Editor screen all unsolicited manuscript submissions and some of these are rejected without further review. All other manuscripts are sent to a minimum of two outside experts for review. After receipt of the reviewers' reports, the Editor-in-Chief and the Emeritus Editor with administrative assistance of the Journal Secretary discuss the merits of the manuscripts and the Editor-in-Chief makes the final decision to accept, reject, or request revision of the manuscript. A request for revision does not guarantee ultimate acceptance of the revised manuscript

Related manuscripts. If there appears to be significant overlap between a manuscript submitted to SAJID and another submitted manuscript by the same authors to SAJID or another journal, the editors will take the matter up with the corresponding author, and based on the response, take appropriate action (ask for modification, or reject with detailed explanation). Further action may include informing the appropriate authority in the authors' resident institution and if overlapping is discovered after

publication in SAJID, publishing an appropriate announcement to that effect in the journal.

DOCUMENT REQUIREMENTS

Checklist

The following are required for your manuscript to be processed:

- Covering letter
- Word count limits
- Conflict of interest statement
- Funding statement
- List of potential reviewers

Covering Letter

All manuscripts submitted to SAJID must be accompanied by a letter declaring that the manuscript has not been submitted or accepted for publication elsewhere. This letter must confirm and declare that all authors have seen and approved the content and have contributed significantly to the work. Authors should suggest potential unbiased reviewers who are qualified to review their manuscript. A covering letter must also accompany a revised submission and must address issues raised in the

review process.

Manuscript Preparation

The SAJID complies with the Uniform Requirements for Manuscripts Submitted to Biomedical Journal Journals (*Ann Intern Med* 2000; 133:229-231 [editorial]; <http://www.icmje.org>, full text). Text, tables, references, and legends must be double-spaced. Italics should be used for genus and species names and for genes but not for *in vivo*, *in vitro*, *in situ*, *et al.*, or other Latin-derived expressions. For layout of manuscript and appropriate style see a recent issue of SAJID.

Title page. On the title page, please supply a running head of not more than 40 characters and spaces, a title of not more than 160 characters and spaces, the names and affiliations of all the authors, and word counts of the abstract and text. Each author's first name, subsequent initials and surname must be used.

Footnote page. Footnotes must include:

- Statement that authors either have or have not a commercial or other association that might pose a conflict of interest (e.g. pharmaceutical stock ownership, consultancy, advisory board membership, relevant patents, or research funding)
- Statement naming sources of financial support (including grant numbers)
- Name, date (month and year), and location (city, and country if not South Africa) of a meeting at which all or part of the information has been presented (include an abstract number, if available)

- Name, address, telephone and fax numbers, and e-mail address of the person to whom correspondence should be addressed
- Current affiliations and addresses for authors whose affiliations have changed since completion of the study

Abstract. The abstract for an Article may be structured with the headings Background, Methods, Results, and Conclusions (250-word limit) or unstructured (200-word limit). Abstracts of Brief Reports should be no more than 100 words. Whether structured or unstructured, the abstract must state the purpose of the research, the methods used, the results, and the conclusions. Do not cite references in the abstract. Include up to 10 key words, separate from the abstract. Please remember that the abstract is particularly useful for literature retrieval purposes.

Text. The text of Articles must be no longer than 3500 words, and that of Brief Reports no longer than 2000 words. The Methods section must include a statement that informed consent was obtained from patients or their parents or guardians, and human experimentation guidelines of the National Department of Health (<http://www.doh.gov.za>) or the South African Medical Research Council (MRC; <http://www.sahealthinfo.org/ethics/index.htm>) and /or those of the authors' institution(s) were followed in the conduct of clinical research or that animal experimentation guidelines (see MRC website above) were followed in animal studies.

References. Articles are generally limited to 50 references, Brief Reports to 15 references. Only works that have been published or accepted for publication can be included in the reference list. Unpublished observations by the authors (authors' unpublished data) personal communications (SP Stanley, personal communication), and manuscripts submitted for publication (J Odendaal, S Coovadia and J Radebe, submitted) should be mentioned parenthetically in the text Please number references in order of appearance; those cited only or first in tables or figures are numbered

according to the order in which the table or figure is cited in the text. Example: If table 3 is cited in the text after reference 20, a new reference cited in table 3 will be reference 21.

References must follow the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (<http://www.icmje.org>, full text). Provide all authors' (or editors') names when there are fewer than 7; for 7 or more, list the first 3 and add "et al." Titles of journals not listed in *Index Medicus* should be spelt out in full. Reference to a doctoral thesis or Master's dissertation should include the author, title, institution, location, year and publication information, if published. For online resources, include a URL and date accessed. Accuracy of references is the responsibility of the authors.

Examples of the proper format are as follows:

Sonnenberg P, Glyn Thomas R, Glynn JR, Shearer S, Godfrey-Faussett, Murray J. Clinical and radiological features of pulmonary disease due to culture-positive *Mycobacterium tuberculosis* or non-tuberculous mycobacteria in South African gold miners. *South Afr J Epidemiol Infect* 2005; 20: 130-135

Marin M, Nguyen HQ, Langidrik JR, et al. Measles transmission and vaccine effectiveness during a large outbreak on a densely populated island: Implications for vaccination policy. *Clin Infect Dis* 2006; 42: 315-319

Strebel PM, Papania MJ, Halsey NA. Measles vaccine. In: Plotkin SA, Orenstein WA, eds. *Vaccines*. 4th ed. Philadelphia: WB Saunders, 2004: 389-440.

Mothibeli KM, McGee L, Smith AM, Klugman KP. Molecular epidemiology of pneumococcal serotype 3 isolates.[abstract ID P56]. In: Programme and Abstract Book of the 1st Joint Congress of the Federation of Infectious Diseases Societies of Southern Africa (Sun City, North-West Province). Johannesburg: Presentations Graphics, 2005: 42.

World Health Organization. Initiative for vaccine research. Available at: http://www.who.int/vaccine_research/diseases/measles/en/. Accessed 1 February 2005.

Acknowledgment(s). The page preceding the references may include a statement thanking those who assisted substantially with work relevant to the study.

Statistical analysis. The statistical analyses used should be identified both in the text and in all tables and figures where the results of statistical comparison are shown.

Units of measure. All Data should be expressed in metric units; use of SI units is encouraged. Use °C for temperature.

Tables and figures. Articles are limited to a maximum of seven inserts (tables and figures combined), Brief Reports to a maximum of two inserts. Data should not be repeated in both a table and a figure. Abbreviations and acronyms used in tables and figures must be explained in the table footnotes and figure legends, even if already defined in the text.

Tables should be numbered in the order of mention in the text. Tables should be typed double-spaced throughout, with no vertical or internal rules. Footnotes and accompanying explanatory material should be kept to a minimum. Footnotes should be placed below the table and designated by superscript lowercase letters (listed in order of location when the table is read horizontally). Each column must have an appropriate heading describing the data in the column below, and units of measure must be clearly indicated. For further instructions on the preparation of tables in Word , consult the Special Instructions for Tables.

Figures should be also numbered in the order of mention in the text and should appear at the end of the manuscript and references. Your figures should be prepared in accordance with the Guidelines for Submission of Artwork. Letters, numbers, and symbols should be clear and of sufficient size to be legible when the figures are reduced. Photomicrographs should have internal scale markers. Figures reproduced

from other publications must be accompanied by permission from the copyright holder. If the manuscript is accepted, the author will be required to send one complete set of glossy, hard-copy figures.

Figure legends should be double-spaced and appear on a separate page preceding the figures. Any abbreviations or symbols used but not defined in the figure itself must be defined in the legend.

Style. Authors are referred to the *American Medical Association Manual of style: A Guide for Authors and Editors* (9th ed., Williams & Wilkins, 1997) and the *Chicago Manual of Style* (15th ed., University of Chicago Press, 2003).

For commercially obtained products mentioned in the text, list the full names of manufacturers. Generic names of drugs and other chemical compounds should be used.

Nomenclature. SAJID recommends the latest widely accepted nomenclature, as set out in documents prepared by recognised international agencies e.g. the *International Journal of Systematic and Evolutionary Microbiology*, *Bergey's Manual of Determinative Bacteriology* (9th ed., revised, Williams & Wilkins, 1993), *Virus Taxonomy – The Classification and Nomenclature of Viruses: Sixth Report of the International Committee on Taxonomy of Viruses* (Springer-Verlag, 1995). The latter document also supplies standard abbreviations for virus species.

Clinical trials registration. All clinical trials must be registered in a registry that is electronically accessible to the public, free of charge. Registration should occur before patient enrolment and the registry's URL and the trial's registration number must be supplied at the end of the manuscript's abstract. For information on acceptable registries, consult the ICMJE Web site, <http://www.icmje.org>. The National Library of Medicine's registry which is free and open to all investigators, generally meets with the requirements of journals for the publication of clinical trials.

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Procedure

Authors are advised to retain a copy of submitted manuscripts, including tables, figures and photomicrographs. The journal is not responsible for manuscripts lost or damaged.

All manuscripts must be submitted online at www.sajei.co.za. Register as an author, login in and click on [CLICK HERE TO FOLLOW THE FIVE STEP SUBMISSION PROCESS](#). The covering letter must please be submitted as a supplementary file. For assistance to upload your manuscript or further instructions please contact Ms Robyn Marais at toc@sajei.co.za.

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1. The submission has not been previously published, nor is it before another journal for consideration (or an explanation has been provided in Comments to the Editor).
2. The submission file is in Microsoft Word, RTF document file format.
3. Where available, URLs for the references have been provided.
4. The text is one and a half-spaced; uses a 12-point font; employs italics, rather than underlining (except with URL addresses); and all illustrations, figures, and tables are placed within the text at the appropriate points, rather than at the end.
5. The text adheres to the stylistic and bibliographic requirements outlined in the [Author Guidelines](#), which is found in About the Journal.
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 - o Word count limits
 - o Conflict of interest statement
 - o Funding statement
 - o List of potential reviewers

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