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A description of HIV prevalence and plasma efavirenz concentrations amongst suicide attempters at Tshepong Hospital in South Africa

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A DESCRIPTION OF HIV PREVALENCE AND PLASMA EFAVIRENZ CONCENTRATIONS AMONGST SUICIDE ATTEMPTERS AT TSHEPONG HOSPITAL IN SOUTH AFRICA

Mzamo Ntsikelelo Mbelle

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand in partial fulfilment of the requirements for the degree of Masters in Medicine (MMed) in the division of Internal Medicine

Johannesburg, 2020

DECLARATION

I, Mzamo Ntsikelelo Mbelle declare that this research report is my own work. It is being submitted for the degree of Master of Medicine (MMed) in the division of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

(signature)

27 day of AUGUST 2020

DEDICATION

Dedicated to my mother, also my mentor and biggest fan Prof Nontombi Mbelle.

ABSTRACT

Background: Efavirenz(EFV) is currently used in first-line regimens for the treatment of HIV infection in most low-to-middle income countries (LMIC). Suicidality, an increasing problem in South Africa may be associated with HIV as well as EFV. The study describes the HIV prevalence amongst non-fatal suicide attempters (NFSA), the proportion of HIV-positive receiving EFV-containing ART regimens and plasma EFV levels in those taking EFV.

Methods: In this prospective study, we enrolled NFSA (aged 18-60) admitted to Tshepong Hospital in the North West Province from October 2017 to July 2018. The Columbia Suicide Severity Rating Scale(C-SSRS) screening tool was used to determine the category of suicidal ideation. We described the proportion on EFV-based ART and measured their EFV concentrations.

Results: Of the 119 participants enrolled, 81.4% were female and 95.3% were of African ethnicity. Their mean age was 28.45 years (range, 18-60), 45.4% were HIV positive and 75.9% were on ART, virtually all (95%) receiving EFV. Using the C-SSRS, 78 (73.6%) were in Category 1. No association was found between HIV serostatus and C-SSRS categories (p= 0.999). The mean EFV plasma concentration was 4.45 mcg/ml and mean concentrations were 6.74, 3.65, 1.48 mcg/ml in participants who had viral load of <40, 40-1000, >1000 copies/ml respectively. There was also no statistically significant difference in C-SSRS suicidal ideation category compared to plasma efavirenz concentration (p=0.266). Of the 119, 116 (98.3%) participants attempted suicide by overdose, 65 (55%) revealed their reason was related to personal issues followed by

relationship issues 55 (46.2%). 29 (24.4%), 20 (16.8%) and 15 (12.6%) participants reported a history of emotional, physical and sexual abuse respectively.

Conclusions: There was a disproportionate number of HIV-seropositive patients amongst non-fatal suicide attempters (NFSA) and most were women. Overdose was the leading mechanism of attempt. Interpersonal factors contribute to suicidal behaviour. We found no associations between suicidal ideation category and HIV serostatus or plasma efavirenz concentration. This is reassuring as EFV remains the backbone of ART regimens in most low-to-middle income (LMIC) countries.

ACKNOWLEDGEMENTS

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Secondly, Ms Nandipha Mmile, Mr Pattamukkil Abraham, Mrs Modiegi Rakgokong and the rest of the Perinatal HIV Research Unit (PHRU) at Tshepong Hospital for assistance with data capturing, IT and logistical support and all the patients who willingly participated in this study. This project would have been impossible without all of you.

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ABBREVIATIONS

ACTG	AIDS Clinical Trial Group
AIDS	Acquired Immune-deficiency Syndrome
ART	Antiretroviral Therapy
CD4	Cluster of differentiation- Type 4 T cell
CRF	Case Report Form
CSIR	Council of Scientific and Industrial Research
CSSRs	Columbia Suicide Severity Rating scale
CYP 2B6	Cytochrome P450 2B6 Enzyme Group
DSM IV	Diagnostic and Statistical Manuel of Mental Disorders, 4th edition
EDTA	Ethylenediaminetetraacetic Acid Tube
EFV	Efavirenz
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee (Medical) - Wits University
LMIC	Low-middle Income Country
NFSA	Non-fatal Suicide Attempt
NHLS	National Health Laboratory Services
NiMMS	National Injury Mortality Surveillance System
nNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
PCR	Polymerase Chain Reaction
PLWH	Persons Living with HIV
SASH	South African Stress and Health Study
VCT	Voluntary Counselling and Testing
VL	Viral load
WHO	World Health Organisation

CHAPTER 1: Introduction

1.1 Background

Recent advances in the management of Human immunodeficiency virus (HIV) have improved the prognosis of this devastating disease into an illness that is treatable, much like diabetes mellitus or hypertension. With the advent of effective antiretroviral therapy (ART) there is an increasing understanding of the pharmacological, clinical, systematic and psychiatric side effects of both individual antiretrovirals and combination regimens.

Efavirenz (EFV), is a frequently prescribed non-nucleoside reverse transcriptase inhibitor (nNRTI) that has been associated with neuropsychiatric side effects which range from hallucinations, sleep disturbances, depression and suicidal ideation. There is a large inter-subject variability, which may be attributed to varying plasma efavirenz concentrations as well as genetic phenotypes.

There is conflicting evidence as to whether EFV and/or EFV-containing ART regimens confer an increased risk of suicidal ideation among patients with HIV and this study intends to explore this association.

1.2 Human Immunodeficiency Virus

In 2015, an estimated 11.2% of the South African population was HIV positive. Statistics South Africa (Stats SA) mid-year estimates report that of the total population of nearly 55 million, the total number of people living with HIV is estimated to be 6,2 million and in adults aged 15–49 years, the prevalence of HIV is 16,6%. (1)

Recent data has shown a decline in new infections from 710,000 (670,000–760,000) in 2000 as compared to 340,000 (310,000–370,000) in 2013. Furthermore, South Africa has experienced a 52% decline in AIDS-related deaths between the years of 2010 and 2013, with 45 per 1000 deaths in 2001 and 31 per 1000 in 2013 attributed to the upscaling of antiretroviral therapy. 13% (12%-13%) of persons living with HIV were on ART in 2010 and this increased to 42% (40%-44%) in 2013. (2)

Over the years, the HIV prevalence has remained relatively stable. The total number of persons living with HIV (PLWH) is estimated to be almost 8 million in 2019, slightly up from 7.4 million in 2013. A percentage of 13.5% of the population is currently estimated to be HIV positive. Encouragingly, the prevalence in the 15-49 age group remains stable while the prevalence in the youth aged 15-24 years has decreased in recent years. (3)

1.3 Suicide

1.3.1 Definition

There is controversy in the definition of suicidality. The World Health Organisation (WHO) has adopted nomenclature ‘suicide’ as a suicidal act that results in death while ‘suicide attempts’ refers to suicidal actions that do not result in death. There should be evidence of suicidal intent, whether implicit or explicit, which is often difficult to establish. (4) Although suicidal behaviour can be defined as lethal (that with a high intent to die), or non-lethal/ non-fatal suicide, (low or no intent to die,) there are inconsistencies with the nomenclature which may lead to failure of identification and subsequent appropriate intervention. (5)

1.3.2 Suicide burden

Suicide has been reported to represent 1.8% of the global burden of disease with the WHO estimating that approximately one million people worldwide commit suicide every year. Although it is approximated that 85% come from low-and-middle-income countries (LMIC), data originating from such countries is scarce. In Africa, the lack of systematic data collection means less than 15% of the population have official suicide statistics. (5, 6)

In South Africa, suicide deaths are increasing. Between the years of 2002 and 2008 the annual prevalence per 100 000 population increased from 12,9 to 14.1, while estimated lifetime prevalence of suicide ideation, plan and attempt has been reported as 9.1%, 3.8% and 1.8% respectively. (6, 7)

1.3.3 Risk factors

Various risk factors have been described in the suicidal population. Most notably, when looking at post mortem and mortality data, psychiatric disorders were found to be more prevalent in the suicidal population as compared to the general population. (7, 8) A meta-analysis showed substance use disorder - specifically opioids, bipolar mood disorder (BMD), borderline personality disorder and depression had significant increase in suicide risk. (8) The South African Stress and Health Study (SASH) showed 61% of people who seriously considered killing themselves in their lifetime had a DSM IV criteria-meeting mental condition. (9)

1.3.4 HIV and suicide

Few studies have described increased suicidality, as manifest by suicidal ideation, suicide attempt as well as completed suicides in patients who are HIV positive. Data collected seems to infer that there is an increased lifetime risk of suicidality, however without focusing on current suicidality with an emphasis on timing; the nature of the attempt as well as any factors that might be in play at that specific time. Badiee et al reported a lifetime suicidal ideation of 26% (405/1560) participants in the study and 13% (204/1560) reported lifetime suicide attempt. Approximately 70% of participants in this study were on ART. Of these 1108, 301 (27%) were on an EFV-containing regimen. Patients who attempted suicide were less likely to be on EFV-containing regimen however this was attributed to prescriber bias, as it was not prescribed to patients with prior psychiatric illness. (10)

A study conducted in Durban found an elevated risk of suicidal behaviour among patients with HIV infection with a peak incidence in patients who were recently diagnosed in the immediate period after voluntary counselling and testing (VCT).

Patients, potentially “at risk”, those with pre-existing mental illness or previous suicidal attempt, should be screened so as to ensure better follow-up and activation of the multidisciplinary team as soon as possible. (11)

A study conducted by Mollan et al found a two-fold increase in suicidality among patients with HIV-1 infection who were randomised to an EFV-containing regimen versus an EFV-free regimen. Suicidality accounted for 62 participants, while attempted or completed suicide accounted for 36% (17/45) in the EFV-containing group and 33% (5/15) in the EFV-free group. The hazard ratio being 2.3 (95% CI: 1.27 to 4.10, p=0.006) in four AIDS Clinical Trials Group (ACTG) antiretroviral-naive studies conducted from 2001 to 2010. (12) This study however had limitations. Three of the 4 the studies were open label which may have contributed to reporter bias while there was also a non-standardised questionnaire regarding suicidal ideation and behaviour.

1.3.5 Severity rating

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a tool developed to define suicidal ideation and/or behaviour. It is a categorical scale which ranges from Category 1 “wish to be dead” to Category 10 “completed suicide.” (13). Further-more, suicidal behaviour or ideation as defined by the C-SSR has been shown to predict an increased incidence of suicidal behaviour prospectively. It is available in over 100 languages and has been implemented in many settings. Several versions have been developed and it has been validated for use in both clinical and research settings. (14)

1.4 Efavirenz

1.4.1 Pharmacology

Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor that is an important component in the treatment of HIV and has been part of the backbone of many ART regimens for the past decade. (15) (16) Elevated plasma EFV levels have been associated with neuropsychiatric side effects while sub-therapeutic levels are associated with treatment failure. A level of <1 mcg/ml was associated with virological failure while level >4 mcg/ml was associated threefold increase in adverse effects. (17) Furthermore the adverse effects have been reported to last up to 200 days post initiation of the drug. (18)

1.4.2 Neuropsychiatric Adverse Effects

EFV has been associated with an increase in neuropsychiatric adverse effects (NPAD) ranging from headache, hallucinations and dizziness to acute mania and psychosis.(19) There are risk factors that may confer an increased risk of these manifestations namely: the presence of pre-existing neuropsychiatric illness, HIV disease stage as well as adverse effects from ART. (16) Further-more, the incidence and severity of NPAD has been shown to be decreased by step-wise dosing of EFV. (20)

1.4.3 Cytochrome polymorphisms

EFV undergoes phase I metabolism by the Cytochrome P450 enzyme CYP 2B6. The 516 G>T polymorphism in the CYP 2B6 gene has been associated with increased plasma efavirenz concentrations and increases the risk for adverse neuropsychiatric effects mentioned above. (21) (22)

CHAPTER 2: Methods

2.1 Study Aim

To describe HIV prevalence amongst non-fatal suicide attempts admitted to Tshepong Hospital, the proportion on ART that are receiving EFV-containing regimens and the proportion with elevated EFV levels. Further- more, it seeks to categorise the level of suicide ideation in the various groups.

2.2 Study Objectives

- To report the HIV prevalence in the study population
- To describe the proportion that are on EFV-based ART that have elevated plasma EFV concentrations
- To compare suicidal severity rating amongst HIV seronegative, seropositive and not receiving EFV-containing regimen, and seropositive on EFV-containing regimens
- To describe the frequency of CYP 2B6 polymorphisms amongst all suicidal patients

2.3 Study Setting

The study was conducted at Tshepong Hospital (Klerksdorp/Tshepong Hospital complex) in the outskirts of Jouberton township in Matlosana Municipality, North West Province. This is a district hospital which also provides tertiary services to the surrounding Dr. Kenneth Kaunda district municipality which has a population of approximately 740 000 inhabitants. It is also a referral centre for the adjacent Dr. Ruth Segomotsi Mompati district municipality with an additional 439 637 inhabitants.

2.4 Study design

This is a cross sectional exploratory study that recruited participants admitted with non-fatal suicide attempts (NFSA), prospectively, between October 2017 and July 2018. After giving consent, participants were enrolled and interviewed with data being recorded on case report form (CRF) and captured both in writing and electronically.

2.5 Participant selection

All adult patients who were admitted to Tshepong Hospital Medical Admissions Ward 4 who met the criteria mentioned below were asked to participate in the study. A few days after admission, when stable, participants were referred to the research team by treating clinicians who were part of the multidisciplinary team addressing their medical and psychosocial needs. Those who did not consent were thus not included and a final cohort of 119 participants was enrolled.

2.5.1 Inclusion criteria

Patients who met the following criteria were included in the study:

- They were at least 18 years old.
- Were willing to undergo voluntary counselling and testing (VCT) for HIV if sere-status was not already known to be positive.

2.5.2 Exclusion criteria

Patients who fulfilled the following were excluded:

- Inability to give informed consent
- Unwilling to test for HIV

2.6 Ethical considerations

Prior to commencement of data collection, ethics approval was obtained from University of Witwatersrand Human Research Ethics Committee (HREC): Certificate number: M170212. Approval was also sought from the North West Province Department of Health and by the Klerksdorp/Tshepong Hospital Complex administration. (Appendix 1)

The aims and objectives were explained to all participants of the study. All potential participants had the right to join or to decline and there was no coercion. All participants were given the right to withdraw from the study at any time. As this is a vulnerable population with often distressed participants, they were only referred by clinicians when their medical and psychosocial needs were addressed and the study team did not interfere with their observations and in-patient therapy. The participants were in appropriate medical and/or psychiatry units with continuous observations and there were no recurrent events.

2.7 Data Collection

Participants were en CRF was used to record variables: demographic/epidemiological data (age, gender, race); HIV serostatus; date of first diagnosis if HIV positive; current and past medications history; including duration treatment on an antiretroviral regimen; co-morbid infections and medications; recall of previous psychiatric history or suicidal attempts: current suicide attempt and method and psychological assessment.

The Columbia-Suicide Severity Rating Scale (C-SSRS) - screening tool was then administered to each participant to define suicidal ideation as well as behaviour. As all the participants in this study were non-fatal suicide attempters, they would fall into Category 9 - “Actual attempt (non-fatal)” and thus only the suicidal ideation section of the screening version of the scale was administered. Therefore, the participant’s categorical grades were that of suicidal ideation - Categories 1- 5.

Routine bloods that were taken (including urea, creatinine, complete blood counts and liver function tests (as done for all suicide attempts in the institution) were sent to the National Health Laboratory Services (NHLS) laboratory and results were recorded on the CRF.

If HIV serostatus was unknown, voluntary counselling and testing VCT was conducted and the status was recorded. If HIV-seropositive, CD4 count and HIV VL was requested as per national guidelines and institutional protocol. If participants were know to be positive, the results were obtained from clinical records. In some instances, they were repeated as per guidelines.

A research sample collected in a standard EDTA tube was sent for PCR to determine CYP 2B6 polymorphisms: 516 G>T, 785 A>G and 983 T>G. The Taq Man system was used to identify the polymorphism with verification using Sanger sequencing. This was done at the Council for Scientific and Industrial Research (CSIR) laboratory in Pretoria.

For all participants who are on an efavirenz-containing regimen, a standard clotted sample was taken to measure plasma efavirenz concentration and shipped to the University of Cape Town laboratory in the division of Clinical Pharmacology. Liquid Chromatography-tandem Mass Spectrometry (LC-MS/MS).

2.8 Data Analysis

Data analysis was performed using the Statistical Products and Service Solutions program (IBM SPSS version 26.0.0.0). Descriptive statistics and frequencies and proportions were used to describe baseline characteristics. Nominal variables were depicted by way of bar or pie charts. For numerical data, measures of central tendency such as mean, median, standard deviation and/or interquartile range (IQR) were used to summarise while students t-test or Analyses of Variance (ANOVA) were used to explore relationships between the data, for example, the association EFV concentration and CSSR ideation. Chi squared test, or Fisher's Exact, where applicable, was used to explore associations between categorical data such as that between HIV serostatus and plasma EFV category.

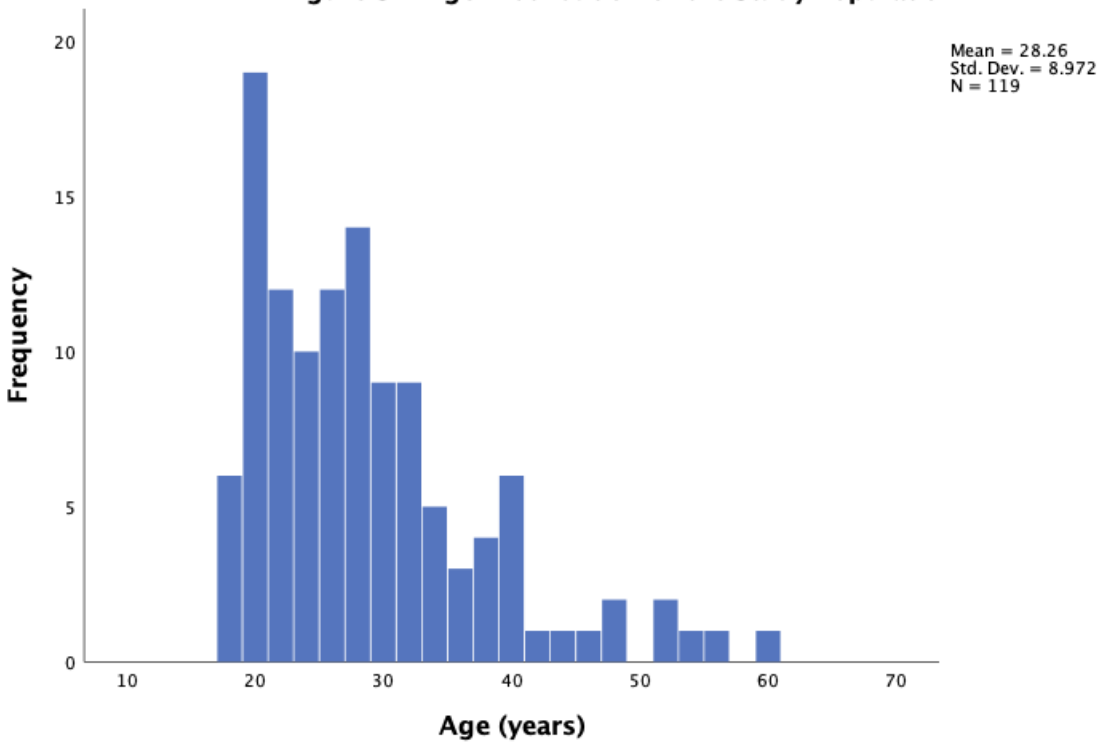
CHAPTER 3: Results

3.1 Patient Demographics

From October 2017 to July 2018 we recruited a total of 119 participants admitted with non-fatal suicide attempts (NFSA) presenting at Tshepong Hospital in this study. Ninety six (81.4%) were women. Further-more,113 (95%) of the participants were African, 3 (2.5%) were Caucasian and 2 (1.7%) were mixed race.

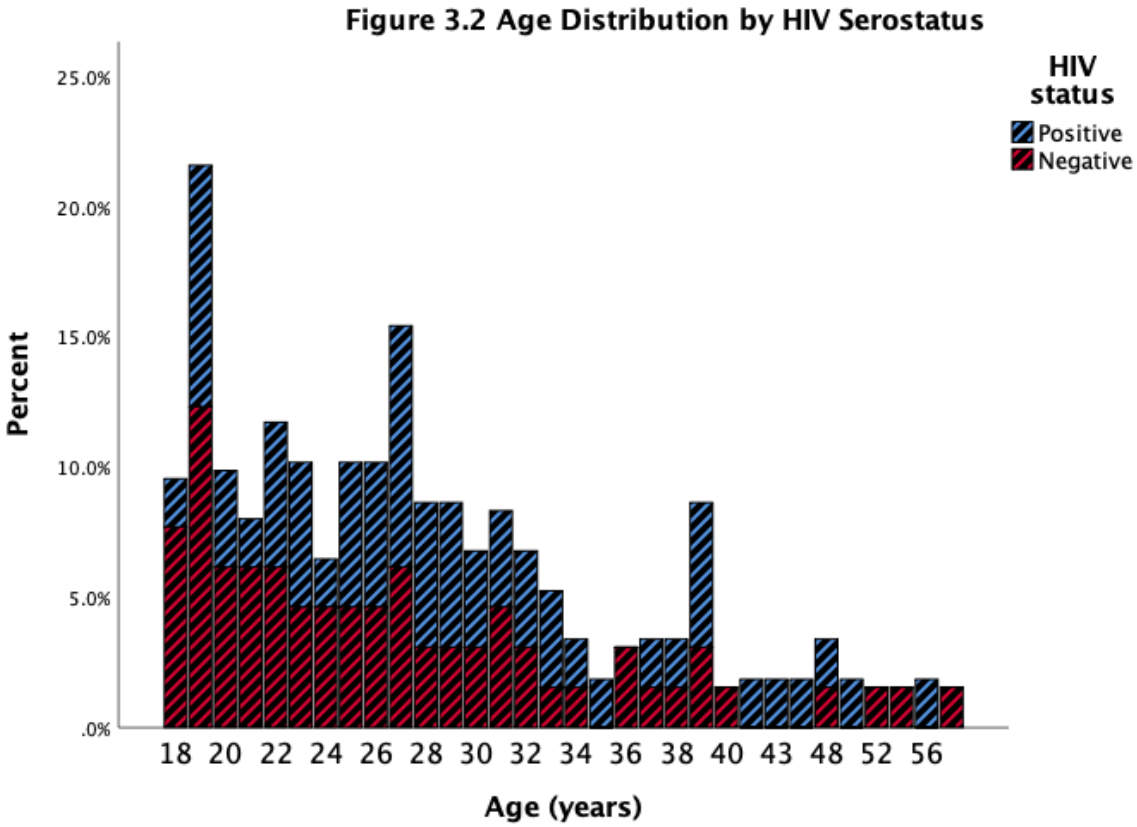
The ages of the participants ranged from 18 to 60 years, with the mean being 28.26 years and median of the data set 27.00 years of age.

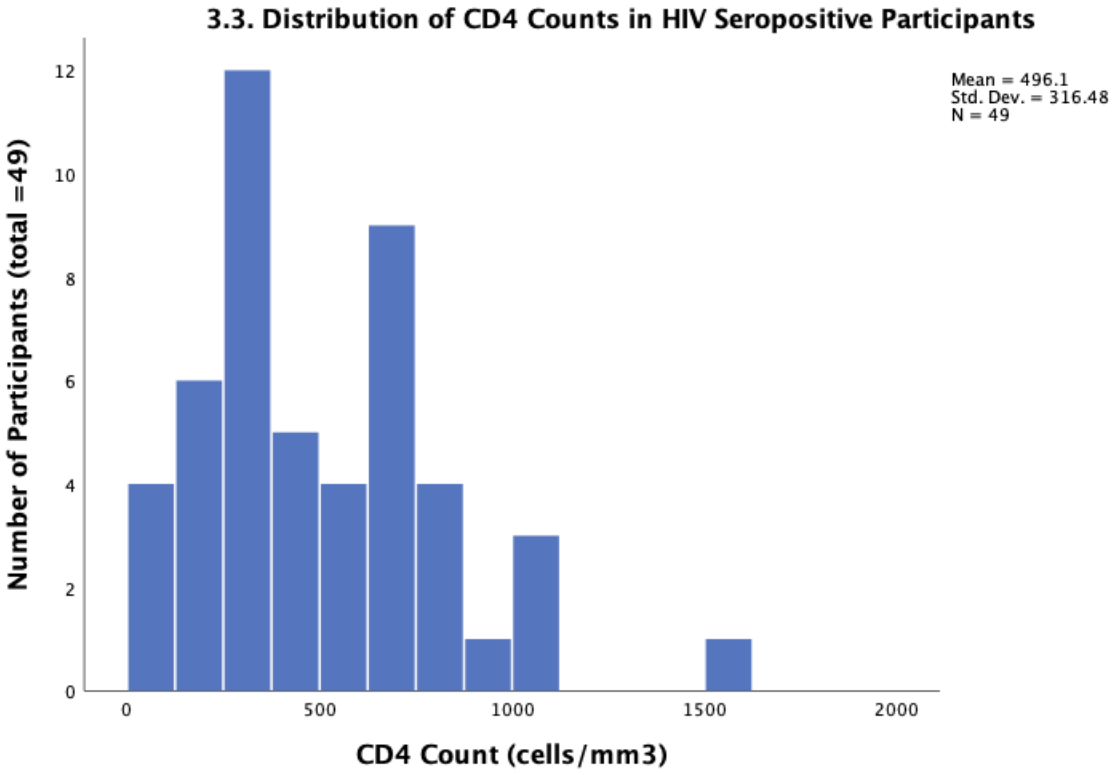
Figure 3.1 Age Distribution of the Study Population



3.2 HIV

In the study population, 54 (45.4%) were HIV seropositive whilst 65 (54.6%) were negative. Forty nine of the HIV positive participants had a CD4 count recorded which ranged from 11 to 1537; the mean (SD) CD4 count was 496 (316) and the median was 415 with a skewness of 0.935. The distribution of HIV serostatus by age followed by the distribution of CD4 counts are depicted graphically below.





Of the 54 participants who were HIV positive, 41 out of 54 (75.9%) were taking ART. The vast majority, 39 out of 41 (95%) were on EFV-based regimen in the form of Odimune or Atripla. This is fixed dose combination (FDC) of tenofovir disoproxil fumarate, emtricitabine and efavirenz (TDF/FTC/EFV). Only one (2.4%) was on the alternate Truvada (TDF/FTC) FDC with nevirapine (TDF/FTC/NVP) and one participant was taking an unknown regimen. HIV VL was drawn for 37 of the 41 participants who had been on ART for a duration of more than six months. 18 (48.6%) participants had a suppressed viral load (<40 copies/ml); 5(13.5%) had a viral load 40-1000 copies/ml while 7 (18.9%) had a viral load above 1000 copies/ml. Seven participants whose viral loads were sent were rejected by the laboratory. This was due to electronic gatekeeping or due to under-filled specimen bottles as reported by the laboratory.

3.3 Suicide

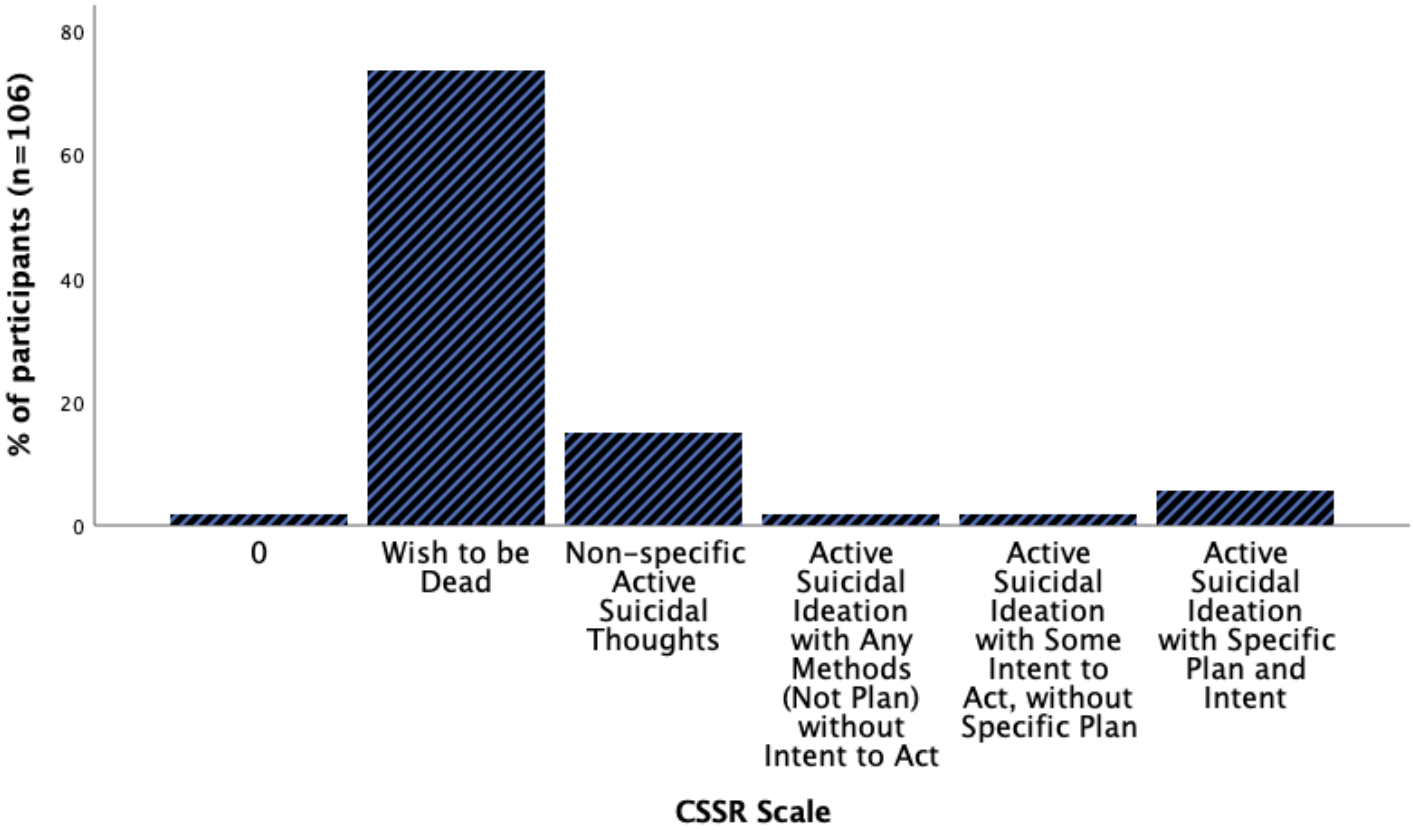
In terms of the method of suicide attempt, there were 116(98.3%) participants who had reportedly taken a drug overdose, 1(0.8%) attempted self- mutilation while for one participant the method was not reported. Twenty five (21.2%) of the participants reported a previous history of a suicide attempt. Fifty five (46.2%) of the total number of participants self-reported that their reason for suicide attempt was relationship issues; 7(5.9%) of the participants reported financial reasons for suicide. Personal issues were reported as a reason for attempt in 66(55.5%) of the participants.

A majority 81(69.2%) of the participants were non-smokers; 35(29.9%) were smokers; while 1 (0.9%) was a previous smoker. Most of the participants reported they did not drink alcohol. There were 52(43.7%) of the total number of participants who drank alcohol, 63(52.9%) never drank alcohol while 4 (3.4%) drank alcohol in the past. There were 110(92.4%) participants who never used marijuana, 6 (5.0%) were previous users while only 3 (2.5%) still report they use marijuana. Four (3.6%) of the total number of participants in the study reported using other recreational drugs.

A total of 50 (42%) participants reported a history of various forms of physical, emotional and psychological abuse; 20 (16.8%) reported a history of physical abuse; 15 (12.6%) of the participants reported a history of sexual abuse; 29(24.4%) reported a history of emotional abuse: 7 (5.9%) and 2 (1.7%) of the total number of participants had a history of financial and verbal abuse respectively. Seventeen out of 50 (34%) had reported more than one type of abuse; 13 (26%) had two types while 2(4%) had reported three and four types of abuse respectively.

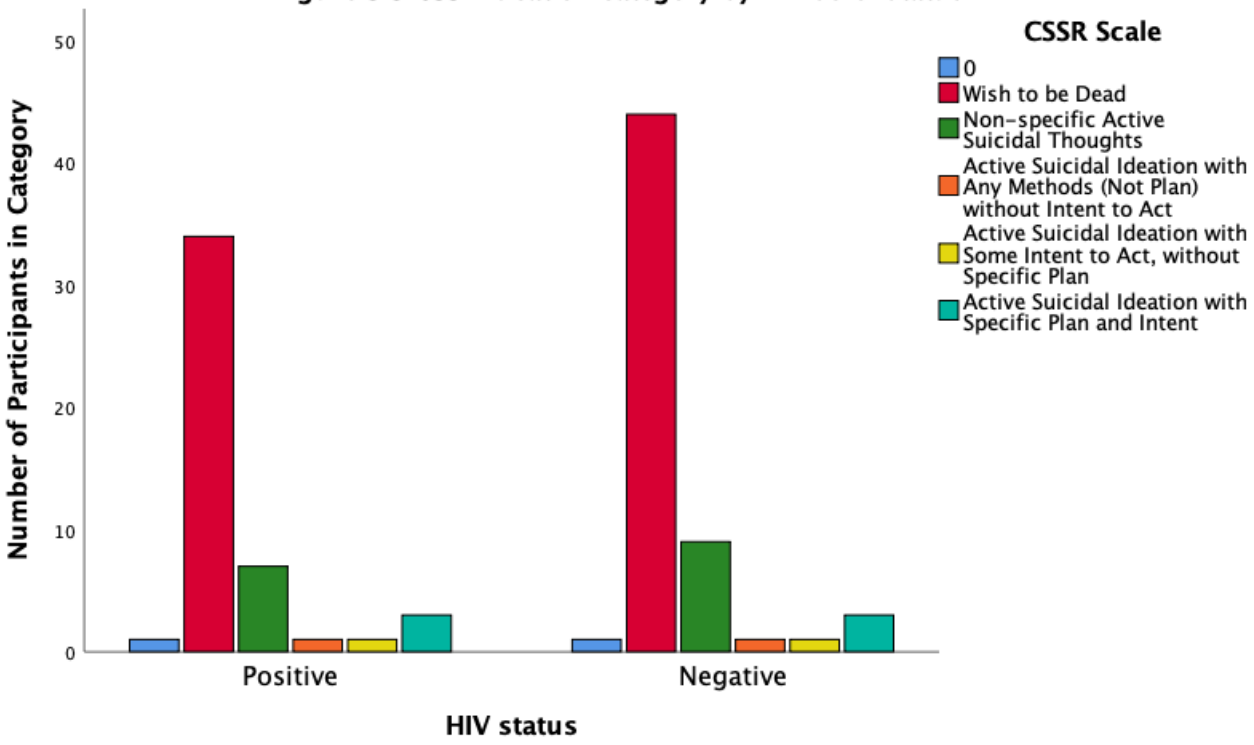
The CSSR screening questionnaire was successfully performed on 106 of the study participants. The majority 78 (73.6%) were in Category 1 - “Wish to be Dead”, 16 (15.1%) were in Category 2 - “Non-specific Active suicidal thoughts”, 2 (1.9%) participants were in Category 3-“Active Suicidal Ideation with Any Methods(not plan) without Intent to Act” as well as Category 4- “Active Suicidal Ideation with Some intent to Act but without a Specific Plan” and a final 6 (5.7%) in the Category 5- “Active Suicidal Ideation with Specific Plan and Intent”. The categories are depicted in the figure below.

Figure 3.4 Proportion of CSSR Categories – Suicidal Ideation



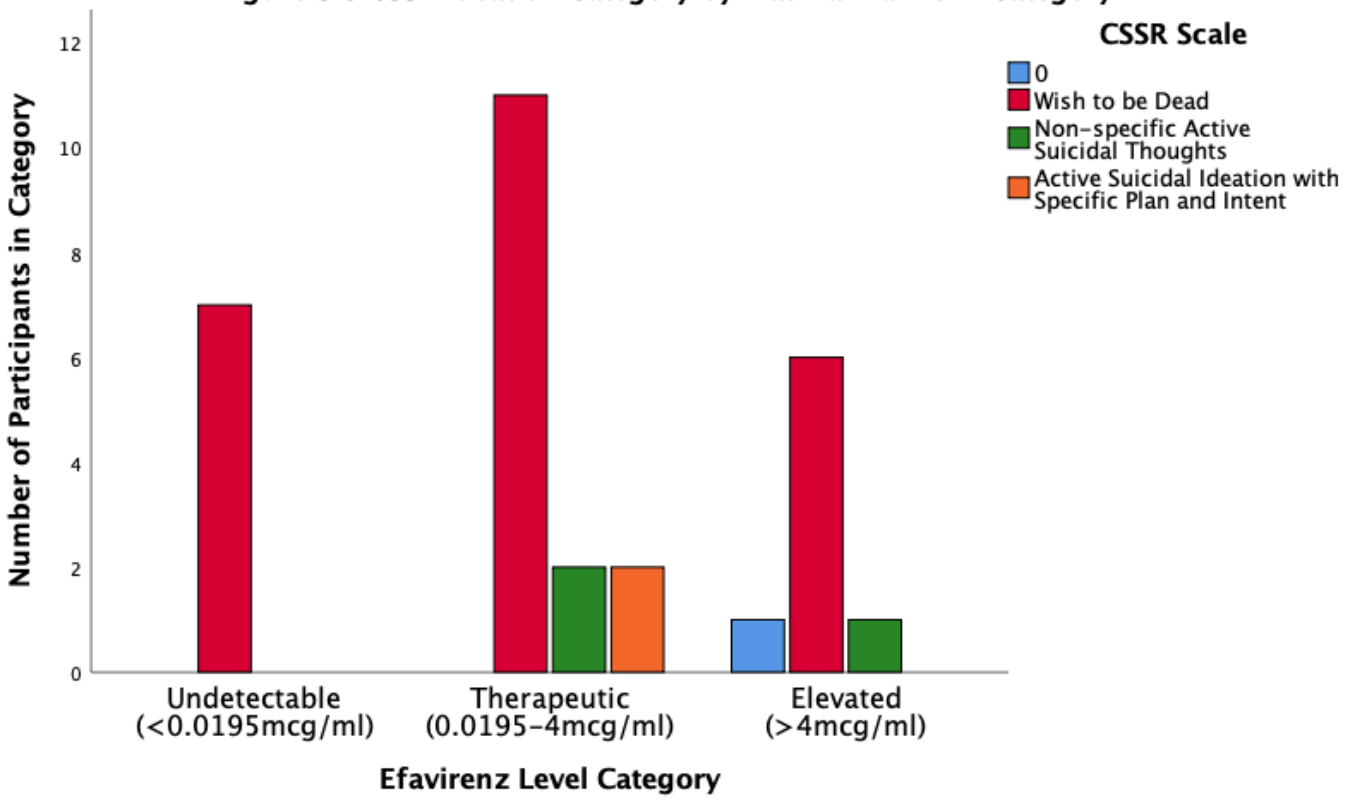
The Chi-Square test was used to assess possible association between HIV serostatus and CSSR category. As the assumption was violated with 8 cells (66.7%) having expected count above the minimum of less than 5, Likelihood ratio was noted to be 0.175 with 5 degrees of freedom and a significance value p=0.999. implying that there was no association between these two variables in this data set.

Figure 3.5 CSSR ideation category by HIV sero-status



Efavirenz level category defined as “Undetectable” which is equivalent to plasma concentration < 0.0195 mcg/ml; “Therapeutic” level between 0.0195 - 4 mcg/ml and “Elevated” which is a level of > 4mcg/ml was compared with CSSR suicidal ideation Category. Again, assumption was violated so the Likelihood ratio was 7.448 with 6 degrees of freedom and a statistical value p 0.281 which does not meet statistical significance.

Figure 3.6 CSSR Ideation Category by Plasma Efavirenz Category

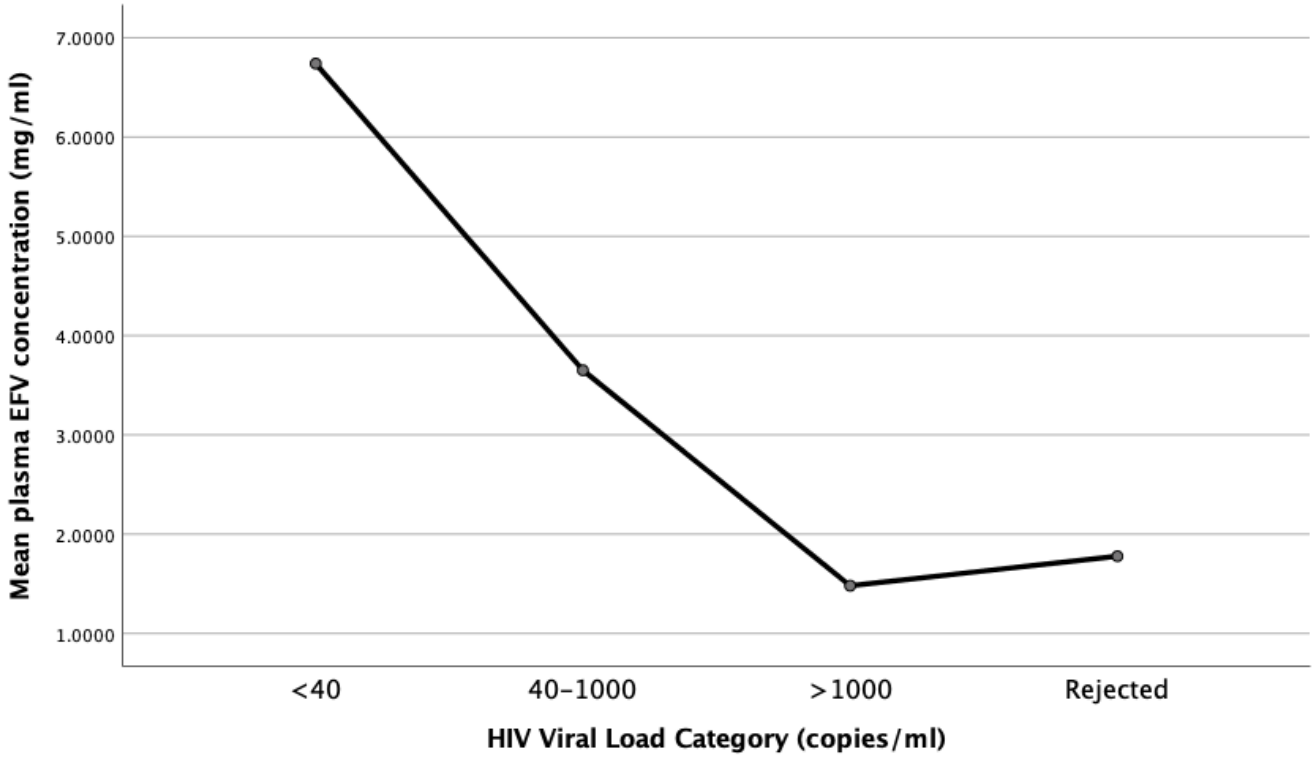


3.4 Plasma efavirenz concentrations

The mean efavirenz (EFV) level for those participants taking the drug (34 participants) was 4.5 mcg/ml, while the standard deviation was 6.4mcg/ml. levels were 6.7, 3.7 and 1.5 mcg/ml for the categories of participants who had HIVVL of <40 , 40-1000 and >1000 copies/ml respectively. The EFV level for the seven whose viral loads were rejected by the lab was 1.8 mcg/ml.

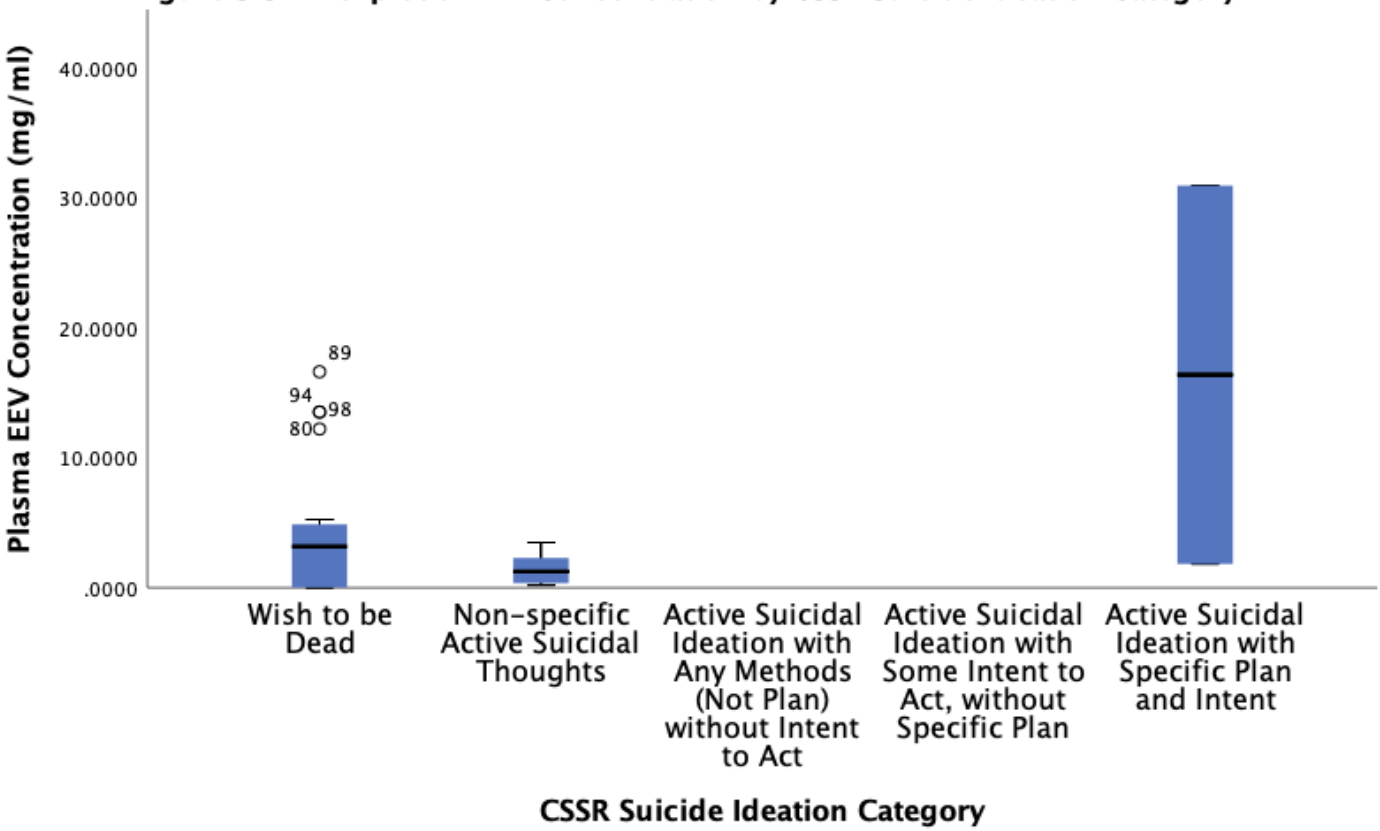
One-way ANOVA was then performed between plasma EFV concentration and HIV VL category. The F statistic was 1.037 (p=0.396) however due to the lack of homogeneity of means, Brown-Forsyth test was performed on this data. F statistic 3.709 (p= 0. 029). There was a statistically significant difference in means between HIV VL categories.

Figure 3.7 Plasma EFV concentration by HIV viral load Category



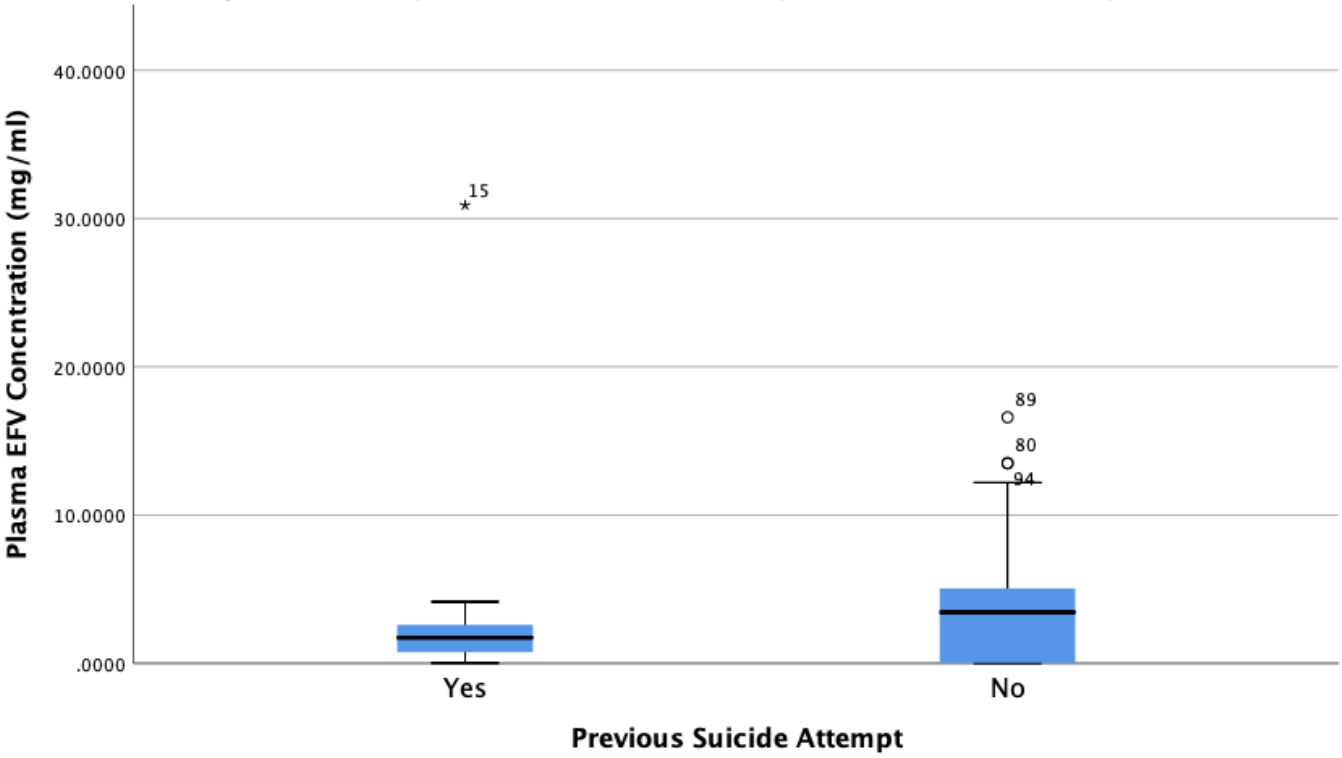
An analysis of variance (ANOVA) was used to compare CSSR - suicidal ideation category to plasma efavirenz concentration. The F-statistic was 4.399 with a p-value 0.023 seemingly implying statistical significance. Levene's test of homogeneity, however showed there was a significant difference in means between the categories and thus more robust tests of equality had to be applied. The Welch as well as Brown-Forsyth tests had F-statistics of 2.315 and 0.816 and yielded p-values 0.266 and 0.612 respectively thus indicating that there was no significant difference in the means/variances amongst the suicidal ideation categories.

Figure 3.8 A Boxplot of EFV Concentration by CSSR Suicide Ideation Category



Analysis of variance (ANOVA) was also used to compare previous suicide attempt to plasma efavirenz concentration in participants taking the drug. The F-statistic was 0.015 with a p-value 0.903. Both the Welch as well as Brown-Forsyth tests had F-statistics of 0.010 and a p-value of 0.921. There was no significant difference in the plasma EFV concentration when comparing previous suicide attempters to those attempting for the first time.

Figure 3.9 A Boxplot of EFV Concentration by Previous Suicide Attempt



3.5 Cytochrome P450 Polymorphisms

Unfortunately, due to an unavoidable time delay between sample collection and processing of specimens, much of the genetic material in serum and plasma was fragmented. Numerous protocols were run to retrieve and/or augment residual genetic material but this was unsuccessful and the material did not meet quality control requirements for analysis. This limitation does not however limit important findings of this study.

Table 3.1 Summary of Descriptive characteristics

Variable	Description	Frequency (n)	Percentage (%)
Gender	Female	96	81.4
	Male	22	18.6
Race	African	113	95.8
	Mixed Race	2	1.7
	Caucasian	3	2.5
Age (years)	mean (SD)	28.3 (8.9)	
Body Mass Index (kg/m2)	mean (IQR)	24.5 (20.1-27.6)	
HIV status	Negative	65	54.6
	Positive	54	45.4
Concurrent TB	No	116	98.3
	Yes	2	1.7
ART Regimen	TDF/FTC/EFV	39	
	TDF/FTCNVP	1	
	Other - Not Specified	75	
Method Current Attempt	Self mutilation	1	0.8
	Overdose	116	98.3
	Other	1	0.8
Psychiatric History	BMD-D	1	0.8
	MDD	1	0.8
	MDE	1	0.8
	NA	116	97.5
Previous Suicide Attempt	No	93	78.8
	Yes	25	21.2
Smoking	No	81	69.2
	Previous	1	0.9
	Yes	35	29.9
Alcohol use	No	63	52.9
	Previous	4	3.4
	Yes	52	43.7
Marijuana	Current	3	2.5
	Never	110	92.4
	Previous	6	5.0

CHAPTER 4: Discussion

4.1 Summary of Results

During the period of October 2017 to July 2018, 119 patients were admitted to the medical admissions ward of Tshepong Hospital with non-fatal suicide attempt and enrolled in the study. There was a female predominance of 81.4% with the vast majority being African, 95%. This hospital serves a predominantly African population. The median age was 27 years, while the range was 18 to 60 years. Of the study population, 54(45.4%) were HIV positive. 41(75.9%) were on ART and 95% (39 out 41) were on an efavirenz-containing regimen.

Of the participants who had their viral load done, 48.6% had an HIV viral load less than 40 copies/ml; 13.5% had VL between 40 and 1000 while 18.9% had viral load above 1000. A further 18.9% had their viral load rejected by the laboratory. The median CD4 cell count was 415 while the range was 11 to 1537. The mean efavirenz plasma concentrations were 6.8, 3.7, 1.5 mcg/ml in those participants who had viral load of <40, 40-1000, >1000 copies/ml respectively and 11.8 mcg/ml in those whose viral load was rejected. There was a significant difference in plasma efavirenz concentration when compared to HIV VL category. (p=0.029)

The vast majority of participants had taken drug overdose 116 (98.3%) as a means of attempting suicide, while only one participant (0.8%) in this study attempted by means of self harm. The data revealed the most common reason for attempt was personal issues 66 (55.5%) followed by relationship issues 55 (46.2%) and then financial reasons 7 (5.9%).

A history of various forms of abuse was also analysed in this study. 29 (24.4%) participants had reported a history of emotional abuse while 20 (16.8%) reported a history of physical abuse. Fifteen (12.6%) of the participants reported a history of sexual abuse. Seven (5.9%) and 2 (1.7%) of the total number of participants had a history of financial and verbal abuse respectively.

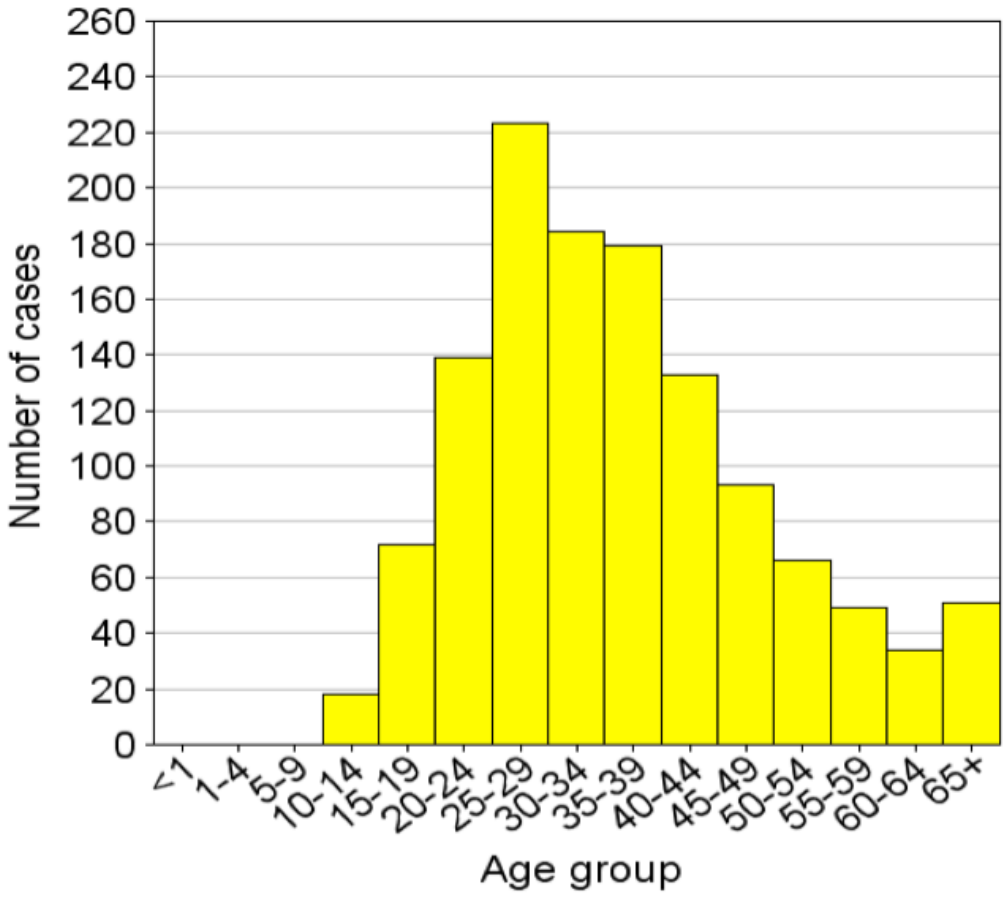
A majority of 78 (73.6%) participants were in Category 1 for CSSR- suicidal ideation. Sixteen (15.1%) were in Category 2. Two (1.9%) participants were in Categories 3 and 4- and a final 6(5.7%) in the Category 5. There was no association between HIV serostatus and CSSR category (p=0.999). There was also no statistically significant difference in means when CSSR - suicidal ideation category was compared to plasma efavirenz concentration (p=0.266).

4.2 Discussion

A total of 119 participants were enrolled in this study. It consisted of 22 (18.5%) males and 96 (81.4%) females. Interestingly, although both international and local data have shown that completed suicide is more common amongst males, suicide ideation with or without intent/plan is more prevalent amongst females, which is evident in the study. (7, 23) This has been previously described as “The Gender Paradox of Suicidal Behaviour”.(24)

The mean age of participants in this study was 28.3 years while the range was from 18 to 60 years. In South Africa, post mortem studies have shown an uneven age distribution in completed suicide. The most recent National Injury Mortality Surveillance System (NIMSS) of 2008 showed that 69.2% of suicide deaths recorded were in age group 15-44 years.

Figure 4.1 Suicide by Age Group Category in years (n=1241)



Within our study population of non-fatal suicide attempters, 45.4% were HIV positive, which is more than two-fold the national HIV prevalence of 19.5% in adults aged 15-49 years old. Few studies have shown an increase in suicidal ideation and or behaviour in people living with HIV (PLWH). Inferential statistics in this study, however, did not show a difference in this study population. When the Chi-Square test was used to assess the possible association between HIV serostatus and CSSR- suicide ideation category, the Likelihood ratio was noted to be 0.175 with 5 degrees of freedom (p=0.999). This study, therefore found no association between suicide ideation category and HIV serostatus. (1) This may be due to the fact that there was selector bias in that all the participants had equal suicide behaviour (namely Category 9 - non-fatal suicide attempt) and thus a larger sample size may be necessary to assess difference in intensity of suicidal ideation. (10)

The vast majority of participants used drug overdose 116 (98.3%) as a means of attempting suicide, while only one participant (0.8%) in this study attempted by means of self harm. Interestingly, when compared to successful suicide, the mode of attempt in the South African context is by means of hanging or gunshot to the head. Bantjes et al (2013) however, found that overdose of medication or poisoning with pesticides is most prevalent amongst females. Furthermore the choice of method is multifactorial, and depends on things like intent, lethality of method, access to method and ethnic or cultural factors. (7) Therefore, as this study comprises predominantly of females, it appears to be consistent with national epidemiological data.

Our data revealed the most commonly reported reason for attempt was personal issues followed by relationship issues. A history of various forms of abuse was also analysed in this study. Empirical data exists on the presence of interpersonal factors in the setting of suicidal behaviour and more testing is required to evaluate possible associations further. (25)

As mentioned earlier 75.9% of HIV-seropositive participants were on ART and 95% of these were on an efavirenz-containing regimen. 48.6% had an HIV viral load which was suppressed, 13.5% had low-level viraemia, while 18.9% had viral load that was not suppressed. The final 18.9% had their viral load rejected by the laboratory. There was also significant difference in EFV concentration amongst the HIV VL groups ($p=0.029$). This would imply there were varying levels of compliance amongst the participants.

Although analysis of variance test showed a significant difference in mean efavirenz plasma concentration as compared to suicidal ideation category, the more robust Brown-Forsyth and Welch tests yielded $p=0.612$ and $p=0.266$ respectively. The data, therefore does not show a correlation between plasma efavirenz concentration and CSSR - suicidal ideation category. One review of 5332 ACTG trial patients showed that patients who were on EFV-based regimen were twice as likely to have suicidal ideation or suicide behaviour than those not-receiving EFV. (12) Subsequent studies however, although showing a higher incidence in depression and other neuropsychiatric side effects, they were unable to find a correlation between EFV and suicide ideation or behaviour. (26, 27)

4.3 Limitations

The cross sectional nature of this study limits the ability to infer causality. This study recruited at a single site and therefore may not be generalisable to other regions of South Africa. Unfortunately, due to fragmentation of DNA material and inability amplify with multiple protocols, we were unable to meet the last objective of describing CYP polymorphisms in this study population. There were also problems with data collection with few missing entries on the data collection sheet at various time points. Restricting recruitment to patients that were admitted may have inadvertently reduced the ability of the study to identify differences in patient groups.

CHAPTER 5: Conclusion

This study showed the prevalence of HIV-seropositive patients amongst non-fatal suicide attempters is higher than national and provincial averages. The female predominance may have contributed to overdose being the predominant mechanism of attempt and it also demonstrated that there are interpersonal factors that may contribute to suicidal ideation or behaviour. The study did not demonstrate associations between suicidal ideation category and HIV sero-positivity or efavirenz plasma concentration.

As suicide and suicide behaviour is increasing in South Africa and HIV remains endemic, we recommend a follow up study specifically designed to better describe the interaction and/or potential causality. A further study would also be needed to describe the prevalence of the CYP 2B6 polymorphisms and the impact they may have on efavirenz metabolism as well as suicidality in the south African context.

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APPENDIX 1: Ethics Approval Certificates

R14/49 Dr Mzamo Mbelle

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170212

NAME: (Principal Investigator)	Dr Mzamo Mbelle
DEPARTMENT:	Internal Medicine Tshepong Hospital
PROJECT TITLE:	A Description of HIV Prevalence, Cytochrome 2B6 Polymorphisms and Plasma Efavirenz Concentrations amongst Suicide Attempters at Tshepong Hospital in South Africa
DATE CONSIDERED:	24/02/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof E Variava and Dr N Martinson
APPROVED BY:	Prof P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	24/07/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in February and will therefore be due in the month of February each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

09/10/2017
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

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Health
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POLICY, PLANNING, RESEARCH, MONITORING AND EVALUATION

Name of researcher : **Dr. M. Mbelle**
University of the Witwatersrand

Physical Address _____
(Work/ Institution) _____
_____

Subject : **Research Approval Letter- A description of HIV prevalence, CYP 2B Polymorphisms and plasma efavirenz concentrations amongst suicide attempters at Tshepong Hospital in South Africa.**

This letter serves to inform the Researcher that permission to undertake the above mentioned study has been granted by the North West Department of Health. The Researcher is expected to arrange in advance with the chosen facilities, and issue this letter as proof that permission has been granted by the Provincial office.

This letter of permission should be signed and a copy returned to the department. By signing, the Researcher agrees, binds him/herself and undertakes to furnish the Department with an electronic copy of the final research report. Alternatively, the Researcher can also provide the Department with electronic summary highlighting recommendations that will assist the department in its planning to improve some of its services where possible. Through this the Researcher will not only contribute to the academic body of knowledge but also contributes towards the bettering of health care services and thus the overall health of citizens in the North West Province.

Kindest regards

Mr. L.P. Moaisi
Acting Director: PPRM&E

04/10/17
Date

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5 OCT 2017
NORTH WEST PROVINCE
REPUBLIC OF SOUTH AFRICA

Researcher

09/10/2017
Date

Healthy Living for All

APPENDIX 2: CSSR-Screening tool

SUICIDAL IDEATION		
Ask questions 1 and 2. If both answers are negative, proceed to "Suicidal Behaviour" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not to be alive anymore, or wishes to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes No**	**Yes** **No**
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes No**	**Yes** **No**
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This differs from a specific plan with time, place, or method details worked out (e.g. thought of method to kill self but not of a specific plan). Includes a person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where, or how I would actually do it… and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes No**	**Yes** **No**
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to, *"I have the thoughts but I definitely will not do anything about them."* ***Have you had such thoughts and had some intention of acting on them?*** If yes, describe:	**Yes No**	**Yes** **No**
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started working out or worked out the details of how to kill yourself? Do you intend carrying out this plan?*** If yes, describe:	**Yes No**	**Yes** **No**
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e. 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation*** Past X Months - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have such thoughts, how long do they last?*** (1) Fleeting - a few seconds or minutes (2) Less than an hour/some of the time (3) 1-4 hours/a lot of the time (4) 4-8 hours/most of the day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____

Deterrents ***Is there anyone or anything (e.g. family, religion, pain of death) that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling), or was it to get attention, revenge, or a reaction from others? Or both?*** (1) Completely to get attention, revenge, or a reaction from others (2) Mostly to get attention, revenge, or a reaction from others (3) Equally to get attention, revenge, or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

APPENDIX 3: Data Collection Sheet

Confidential

Efavirenz Suicide Study [Dr. Mzamo Mbelle]

_____

Yes No

Yes No

_____

_____

Male Female

_____

_____

Black White Coloured Asian Other

_____

_____

(_____kg)

_____

(_____cm) _____

Positive Negative Unknown

_____

_____

_____

Data Collection Instrument

Study Number

1. Eligibility

1.1. Did the participant sign consent?

1.2. Did the participant fulfill eligibility criteria?

2. Baseline Characteristics

2.1. Date of birth Age
2.1.1 Gender

2.2. Date of admission
2.3. Date of discharge
2.4. Date deceased (if deceased) 2.5. Race

2.5.1. Describe other

- 2.6. Weight

- 2.7. Height

BMI
2.8. HIV serostatus

2.8.1. Date tested 2.9. CD4 count 2.9.1. Date tested 2.10. Viral load 2.10.1. Date tested

2.11. ART regimen

TDF + FTC/3TC + EFV or Atripla/Tribuss TDF + FTC/3TC + DTG
ABC + FTC/3TC + EFV
TDF + FTC/3TC + NVP

ABC + FTC/3TC + NVP
ZDV + FTC/3TC + NVP
TDF + FTC/3TC + LPV-r
ABC + FTC/3TC + LPV-r
ZDV + FTC/3TC + LPV-r
TDF + FTC/3TC + ATV-r
ABC + FTC/3TC + ATV-r
D4T + FTC/3TC + EFV
D4T + FTC/3TC + NVP

D4T + FTC/3TC + LPV/r
D4T + FTC/3TC + ATV-R TDF + FTC /3TC + Rilpivirine ABC + FTC/3TC + Rilpivirine ZDV + FTC/3TC + Rilpivirine D4T + FTC/3TC + Rilpivirine

_____

TDF + FTC/3TC + EFV or Atripla/Tribuss TDF + FTC/3TC + DTG
ABC + FTC/3TC + EFV
TDF + FTC/3TC + NVP

ABC + FTC/3TC + NVP
ZDV + FTC/3TC + NVP
TDF + FTC/3TC + LPV-r
ABC + FTC/3TC + LPV-r
ZDV + FTC/3TC + LPV-r
TDF + FTC/3TC + ATV-r
ABC + FTC/3TC + ATV-r
D4T + FTC/3TC + EFV
D4T + FTC/3TC + NVP
D4T + FTC/3TC + LPV/r
D4T + FTC/3TC + ATV-R TDF + FTC /3TC + Rilpivirine ABC + FTC/3TC + Rilpivirine ZDV + FTC/3TC + Rilpivirine D4T + FTC/3TC + Rilpivirine

_____

Yes No

RHZE RH ME MDR Other

_____

Hypertension Diabetes Cancer
Thyroid disease Epilepsy

Other _____

2.11.1. Date commenced 2.12. Previous regimen

2.12.1. Date commenced 2.13. Concurrent TB

2.14. Tuberculosis treatment

2.14.1. Describe other
2.15. Medical co-morbidities (excluding TB)

2.15.1. Cancer - specify

Confidential

2.15.2. Describe other
2.16. Number of current medications (excluding TB) 2.16.1. Medication 1
2.16.1.1. Dose

2.16.2. Medication 2
2.16.3. Medication 3
2.16.4. Medication 4
2.16.5. Medication 5
2.16.6. Medication 6
2.16.7. Medication 7
2.16.8. Medication 8
2.17. Previous psychiatric diagnosis

_____

_____

(_____.__mg) _____
_____ _____
_____ _____

Schizophrenia
Schizoaffective disorder, bipolar type
Bipolar 1 disorder. depressed
Bipolar 1 disorder. maniac
Bipolar and related disorder due to another medical condition
Cannabis use disorder
Depressive disorder due to another medical condition
Inhalant intoxication
Major depressive disorder, recurrent episode Major depressive disorder, single episode
Other

_____

Schizophrenia
Schizoaffective disorder, bipolar type
Bipolar 1 disorder. depressed
Bipolar 1 disorder. maniac
Bipolar and related disorder due to another medical condition
Cannabis use disorder

Depressive disorder due to another medical condition
Inhalant intoxication
Major depressive disorder, recurrent episode Major depressive disorder, single episode
Other

_____

2.17.1. Describe other
2.18. Current psychiatric diagnosis

2.18.1. Describe other



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3. Stressors

3.1. Lives with

3.1.1. Describe other 3.2. History of abuse

3.2.1. Describe other 3.3. Abused by

3.3.1. Describe other 3.4. Incarceration

3.4.1. Date begun 3.5. Smoking history

3.5.1. Number of cigarettes per day 3.6. Alcohol use

3.6.1. Number of units per week 3.7. Marijuana use

3.8. Other habit(s)? 3.8.1. Describe other

Both parents Biological mother Biological father Adopted family Maternal family
Paternal family Sexual partner Alone

Spouse Other

_____

Physical
Sexual
Emotional
Financial
Restriction of access to others Other

Mother
Father
Sexual partner Prior sexual partner Family member Teacher
Colleague at work Other

Previous Current Never

Yes
No Previous

Yes
No Previous

(1 Unit = 1x350ml Beer; 1xglass of wine; 1x25ml measure, spirits)

Current Previous Never

Yes No

---

4. Suicide history/attempt

4.1. Previous suicide attempt?

4.1.1. Date of attempt
4.2. Reason for previous attempt

4.2.1. Describe other
4.3. Treatment for previous suicide attempt

4.4. Method of previous attempt

4.4.1. Describe other
4.5. Prior suicide attempt in family?

4.5.1. Date of attempt
4.6. Current suicide attempt?

4.6.1. Date of attempt
4.7. Reason for current attempt

4.7.1. Describe other
4.8. Method of current attempt

4.8.1. Describe other
4.9. Duration of symptoms prior to attempt

4.10. Columbia suicide severity rating

Yes No

_____

Family Relationship Financial Personal Other

_____

Psychiatric hospital, in-patient Psychiatric, out-patient Family
Traditional healer

NIL

Overdose Hanging Self-mutilation Gun

Knife Other

_____

Yes No

_____

Yes No

_____

Family Relationship Financial Personal Other

_____

Overdose Hanging Self-mutilation Gun

Knife Other

_____

_____

(_____days) _____



5. Laboratory investigations

5.1. Plasma efavirenz concentration

5.2. Last EFV dose taken
5.3. Cytochrome P450 polymorphism

5.4.1. Urea:
5.4.2. Creat:
5.4.3. Na+:
5.4.4. K+:
5.4.5. Cl-:
5.4.6. eGFR:
5.4.7. TBil:
5.4.8. dBil:
5.4.9. Tprot:
5.4.10. Alb:
5.4.11. ALP:
5.4.12. GGT:
5.4.13. Alt:

5.4.14. AST:
5.4.15. Hb:
5.4.16. MCV:
5.4.17. WCC:
5.4.18. PLT:
5.4.19. INR:
5.4.20. PTT:
5.4.21. tChol:
5.4.22. TG:
5.4.23. HDL:
5.4.24. LDL:
6.1. Date of CRF completion
6.2. Initials of person completing the CRF

_____

(_____ucg/L (XXX if not taken)) _____

516 T>G 983 T>G 785 A>G 15582 C>G

_____

_____



Confidential

Audit Trail

Name of Data Entry person Date of Data Entry

_____

(Initial.Surname) _____

(Kindly change the date every time a change is made to this Form)

