

Influence of Social Psychological Status On Efavirenz And Nevirapine Plasma Concentration Among HIV Patients In Kenya

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Research Article

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Abstract

HIV-related stigma, lack of disclosure and social support are still a hindrance to HIV testing, care, and prevention. We evaluated the influence of these socio-psychological status on nevirapine (NVP) and efavirenz (EFV) plasma concentrations among HIV patients in Kenya. Blood samples were obtained from 254 and 312 consenting HIV patients on NVP and EFV based first-line Antiretroviral therapy (ART) respectively and a detailed structured questionnaire was administered. The NVP and EFV plasma level was measured by liquid chromatography - tandem mass spectrometry (LC-MS/MS). The median duration of living with HIV infection was 5 years (IQR = 1–11 years) and a median duration since ART initiation was 3 years (IQR = 1–8 years). There were 68.1% and 65.4% of the patients on NVP and EFV respectively who did not feel guilty for being HIV positive. The disclosure rate was about 96.1% and 94.6% of patients on NVP and EFV respectively. About 85% and 78.2% of patients on NVP and EFV respectively who got social support as much as needed. The non-adherence to ART in the past 30 days was 64.6% and 66.3% patients on NVP and EFV respectively. The median (IQR) plasma concentration were [6237.5 ng/mL, IQR 45188–8964 ng/mL] for NVP and [2739.5 ng/mL, IQR 1878 –4891.5 ng/mL] for EFV. There were 14.2% and 4.5% patients on NVP and EFV respectively with suboptimal plasma concentration associated with poor viral suppression. Multivariate linear regression analysis showed feeling guilty for being HIV positive (adjusted $\beta = 954$, 95% CI = 192.7 to 2156.6; $p = 0.014$) or feeling worthless for being HIV positive (adjusted $\beta = 852$, 95% CI = 64.3 to 1639.7; $p = 0.034$); being certain of telling the primary sexual partner about HIV positive status (adjusted $\beta = 363$, 95% CI, 97.9 to 628.1; $p = 0.007$); disclosing HIV status to neighbors (adjusted $\beta = 1731$, 95% CI = 376 to 3086; $p = 0.012$) and getting transportation to hospital whenever needed (adjusted $\beta = -1143.3$, 95% CI = -1914.3 to -372.4; $p = 0.004$) were associated with NVP/EFV plasma levels. The NVP and EFV plasma level was highly heterogeneous with a significant proportion of patients reporting levels correlated with poor viral suppression. The patient's stigma, lack of disclosure and social support contributes significantly on the overall ART treatment outcome. Taking these factors into consideration, HIV treatment may be personalized to achieve optimal treatment success

Introduction

Although the current trend on global HIV epidemic has stabilized, data imply disappointingly high level of infection, an indictment of irregular control progress in countless countries [1]. The HIV pandemic continues to be the leading cause of death in sub-Saharan Africa with Kenya having the joint third-largest HIV epidemic in the world (alongside Tanzania) with 1.6 million people living with HIV [1]. HIV infection affects every breadth of human's life including physical, psychological, social and spiritual dimensions [2, 3]. In as much as HIV infection has been reported in Kenya for the last four decades, this infection is still dreaded by many mainly due to misinformation about the disease and consequently the stigma and exclusion associated with the infection [4]. People living with HIV (PLWHA) are charged with both medical and social problems associated with the disease [5]. HIV infection among large population, results in stigma both for those infected and affected [6, 7]. Further, infection consistently results in loss of socio-economic status, employment, income, housing, health care and mobility. The outcome of stigma includes but not limited to increased secrecy (lack of disclosure) and denial, which is not only a stimulus for HIV transmission, but also a cause for poor disclosure and subsequent lack or inadequate social support [5, 7].

Antiretroviral therapy (ART) is an integral component in reducing the burden of HIV. Globally, at the end of 2020, 67% of 38 million PLWHA were on ART [1]. Remarkable scale up of ART has put Kenya on track to reach the target on AIDS-related deaths. At the end of 2020, about 74% of adults and 73% of children in Kenya needing ART were essentially receiving it [1]. A remarkable fraction of these patients (68%) had attained viral suppression (UNAIDS, 2020). At the time of this study, the first-line ART guidelines for children, youth and adults in Kenya typically contained a backbone of two

nucleoside reverse transcriptase inhibitors (NRTIs; zidovudine [AZT], or tenofovir [TDF] with lamivudine [3TC]), plus one non-nucleoside reverse transcriptase inhibitor (NNRTI), either nevirapine (NVP) or efavirenz (EFV) [8].

Therapeutic drug exposure is a major requirement for ART management [9]. Suboptimal exposure to ART, especially NNRTIs (NVP and EFV), jeopardizes ART treatment success [10]. Generally, efavirenz and nevirapine plasma concentrations are influenced by several factors including host pharmacogenetics as well as pharmacoecological factors such as ART adherence [11]. The pharmacoecologic factors are those primarily affect adherence including lifestyle, stigma and disclosure among others. HIV stigma negatively affects ART utilization and the quality of care [5]. Social support and disclosure have been shown to significantly affect treatment outcomes in many settings [4]. Counselling and social support for both the infected and affected people is associated with effective coping with each stage of the infection and enriches the quality of life and hence adherence to ART [2]. This study, evaluated the influence HIV stigma, disclosure and social support on ART adherence and the steady-state plasma concentrations of NVP and EFV among HIV patients receiving ART in one of the largest and oldest cosmopolitan care and treatment centers in Kenya.

Methods

Study design and setting

This was a cross-sectional study conducted between August, 2016 to January 2020. Data presented in this study was part of a study that aimed at assessing the pharmacogenetic and pharmacoecologic etiology of sub-optimal responses to non-nucleoside reverse transcriptase inhibitor (NNRTI) among HIV patients in Nairobi, Kenya. Patients were recruited in this study if they were; HIV infected adults (aged above 18 years); receiving first line ART comprising of AZT or ABC, 3TC, and EFV or NVP for at least 12 months at the Family AIDS Care and Educational Services (FACES) based at Kenya Medical Research Institute (KEMRI) in Nairobi Kenya and were willing to give voluntary written informed consent. The study population and site has been described in detail in our previous publication Ngayo et al., [12]. This research was carried out in accordance with the basic principles defined in Guidance for Good Clinical Practice and the Principles enunciated in the Declaration of Helsinki (Edinburg, October 2000). This protocol and the corresponding informed consent forms used in this study were reviewed and permission obtained from, the Kenya Medical Research Institute Scientific Review Unit (SERU) (Protocol No SSC 2539). Written informed consent was obtained from all participants before enrollment.

Sample size

Sample size calculation used the formula described by Lemashow [13] based on population proportion estimation with specified relative precision. The alpha (α) was set at 0.05, relative precision (ϵ) at 0.20 and proportion of HIV infected individuals with sub-optimal NVP/EFV plasma levels during a 12-month ART at 15% (14, 15). A total of 599 participants were recruited to achieve 0.95 power where by recruitment of patients per treatment arm was done proportionate to size yielding 269 and 330 patients on NVP and EFV respectively.

Data collection

An exhaustive structured interview was used to collect patient-related information from all the study patients. The data collected included demographic characteristics, clinical history, adherence and HIV stigma. A pilot study had been conducted to test the questionnaire and other key points in the interviews. Some of the key points explored in the structured questionnaire included stigma and segregation of people living with HIV (self-worth, guilt, emotional feeling); challenges of living with HIV, such as access to health services and community life; experiences/issues with the HIV disclosure and adherence to medications. The interviews were conducted by a clinician in a separated private room.

The second part of the questionnaire was filled by retrospective review of patient medical records to abstract data on occurrence of any adverse drug reactions, evidence of treatment failures, adherence to clinic appointments.

Whole blood samples (5 mL) at 12–16 hours post ARV uptake was collected using EDTA anticoagulant tubes for determining the concentration of NVP and EFV plasma concentration.

Determination of nevirapine and efavirenz plasma concentrations

The nevirapine and efavirenz plasma concentrations were measured at the laboratory using a tandem quadrupole mass spectrometer (LC/MS/MS) designed for ultra-high performance: Xevo TQ-S (Waters Corporation, U.S.A) as described by Reddy *et al.* [16]. Plasma samples were first subjected to a thorough in-house method for the inactivation of the HIV virus. Plasma samples were extracted using the Bond Elut C18 cartridges according to manufacturer's instructions (Agilent Technologies, USA). The Eluents were then completely evaporated using Thermo Scientific™ Reacti-Vap™ Evaporators (Thermo Fisher Scientific Inc, USA) at 37 °C for 30 min. This was then reconstituted using 100µl of equal parts 1:1 acetonitrile and water, vortexed briefly and transferred into 50ml capped vials and placed into Xevo TQ-S (Waters Corporation, U.S.A) for quantification. About 1µl of the samples was injected automatically into the LC/MS/MS instrument and quantified within 5 minutes

Data analysis

All data were subjected to descriptive data analysis. Frequencies and percentages were used to present the sociodemographic data. HIV stigma, disclosure and social support related factors influences the drug plasma concentrations through drug adherence. The association between these variables and ART drug adherence was first evaluated using chi-square or Fishers exact test. Significant variables were then analyzed for association with NVP and EFV plasma levels. Steady-state NVP and EFV plasma concentrations were not normally distributed by the Shapiro- Wilk test, hence Kruskal-Wallis test and Dunn's test and quantile regression analysis were used to evaluate variations and association with NVP and EFV plasma levels at 5% significance level. All statistical analyses were performed using STATA v 13 (StataCorp LP, Texas, USA). The NVP plasma concentration was categorized as < 3100 ng/mL (below therapeutic range), 3100–4300 ng/mL (therapeutic range) and > 4300 ng/mL (above therapeutic range). For EFV, the concentrations of < 1000 ng/ml was considered below therapeutic range, 1000 to 4000ng/ml considered therapeutic range and > 4000 ng/ml considered suprathreshold level [17, 18].

Results

Baseline characteristics of study participants

Table 1 summarizes the baseline characteristics of study population. The results from the 254/269 (94.4%) and 312/330 (94.5%) response rate of patients on NVP and EFV respectively with all the relevant data were analyzed. The median age of the patients was 41 years (IQR = 35–47 years), with a median duration of living with HIV infection of five years (IQR = 1–11years) and a median duration since ART initiation of three years (IQR = 1–8 years). Among these patients 342 (60.4%) were female, 379 (67%) were married, 367(64.8%) were Bantus, 106 (18.2%) had a previous partner who died. Only 3.5% and 5.8%; 19.7% and 17.3% (on NVP and EFV respectively) were currently smoking and taking alcohol respectively. Out of 254 patients on NVP and 312 on EFV, majority 74.4% and 73.3% stated the difficulties disclosing their HIV status. On the contrary, the majority 79.1% and 75.9%; 68.1% and 65.4% (on NVP and EFV respectively) did not feel immoral or guilty for being HIV positive, respectively. Both patients on NVP and EFV, majority did not feel ashamed or worthless for being HIV positive and were very ready to tell their primary sexual partner of their HIV status. The majority 85% (NVP) and 78.2% (EFV) got as much as would like useful advice about important things in life (p = 0.022). Similarly, the majority of these patients got as much as possible chance to talk to someone about

work/household problems, about personal/family problem, people who cared about their situations and got as much love and affection. Majority of the patients also got emergency financial and transportation support but there was no significant difference by ART regimen. Other than age ($p = 0.046$) and number of life sexual partners ($p = 0.019$), there was no significant difference in the baseline characteristics between patients on NVP and those on EFV.

Table 1. Baseline characteristics of the study patients

Variable	All Patients (n = 566)		Nevirapine (n = 254)		Efavirenze (n = 312)		p Value
	n	(%)	n	(%)	n	(%)	
Age (years)	Median (IQR)	41 (35 - 47)	42 (36 - 48)	40 (34 - 47)			0.046
	20-30	66 (11.7)	25 (9.8)	41 (13.1)			
	31-40	210 (37.1)	84 (33)	126 (40.4)			
	41-50	202 (35.7)	106 (41.7)	96 (30.8)			
Gender	>51	88 (15.5)	39 (15.4)	49 (15.7)			0.102
	Female	342 (60.4)	163 (64.2)	179 (57.4)			
Marital status	Male	224 (39.6)	91 (35.8)	133 (42.6)			0.703
	Married	379 (67)	165 (65.0)	214 (68.6)			
	Single	154 (27.2)	72 (28.4)	82 (26.3)			
	Divorced	26 (4.6)	14 (5.5)	12 (3.9)			
Occupation	Widow	7 (1.2)	3 (1.2)	4 (1.3)			0.354
	Employed	193 (34.1)	80 (31.5)	113 (36.2)			
	Unemployed	102 (18)	44 (17.3)	58 (18.9)			
Ethnicity	Self employed	271 (47.9)	130 (51.2)	141 (45.2)			0.256
	Bantu	367 (64.8)	161 (63.4)	206 (66.0)			
	Nilotes	190 (33.6)	91 (35.8)	99 (31.7)			
	Cushites	9 (1.7)	2 (0.8)	7 (2.2)			
Education level	Primary	174 (30.7)	69 (27.2)	105 (33.4)			0.17
	Secondary	203 (35.9)	102 (40.2)	101 (32.4)			
	Tertiary	182 (32.2)	81 (31.9)	101 (32.4)			
	Non-formal	7 (1.2)	2 (0.8)	5 (1.6)			
Cigarette smoking	Yes	27 (4.8)	9 (3.5)	18 (5.8)			0.24
	No	539 (95.2)	245 (96.5)	294 (94.3)			
Alcohol consumption	Yes	104 (18.4)	50 (19.7)	54 (17.3)			0.099
	No	462 (81.6)	204 (80.3)	258 (82.7)			
Age of sexual debut (Years)	Median (IQR)	18 (17 - 20)	18 (17 - 19)	18 (17 - 20)			0.929
	<18	371 (65.6)	166 (65.4)	205 (65.7)			
	>18	195 (34.5)	88 (34.7)	107 (34.3)			
Lifetime sexual partners	Median (IQR)	2 (1-5)	2 (1 - 4)	3 (1 - 5)			0.019
	None	3 (0.5)	2 (0.8)	1 (0.3)			
	1	214 (37.8)	110 (43.3)	104 (33.3)			
	>1	349 (61.7)	142 (55.9)	207 (66.4)			
Current ART regimen	3TC, ABC, EFV	1 (0.2)	0 (0)	1 (0.3)			0.0001
	3TC, TDF, EFV	187 (33.1)	0 (0)	187 (59.9)			
	3TC, ZDV, EFV	124 (21.9)	0 (0)	124 (39.7)			
	3TC, ABC, NVP	1 (0.2)	1 (0.4)	0 (0)			
	3TC, TDF, NVP	159 (28.1)	159 (62.6)	0 (0)			
	3TC, ZDV, NVP	93 (16.4)	93 (36.6)	0 (0)			
	3TC, d4T, NVP	1 (0.2)	1 (0.4)	0 (0)			
Difficult to tell others about my HIV infection	Agree	418 (73.8)	189 (74.4)	229 (73.4)			0.848
	Disagree	148 (26.2)	65 (25.6)	88 (28.0)			
Feeling guilty for being HIV positive	Agree	189 (33.4)	81 (31.9)	108 (34.6)			0.531
	Disagree	377 (66.6)	173 (68.1)	204 (65.4)			
Feeling worthless for being HIV positive	Agree	137 (24.2)	55 (21.7)	82 (26.3)			0.236
	Disagree	429 (75.8)	199 (78.4)	230 (73.7)			
Hide HIV status from others	Agree	403 (71.2)	186 (73.2)	217 (69.5)			9.352
	Disagree	163 (28.8)	68 (26.8)	95 (30.5)			
Disclose HIV status to anyone	Yes	539 (95.2)	244 (96.1)	295 (94.6)			0.435
	No	27 (4.7)	10 (3.9)	17 (5.4)			
Disclosed HIV status to partner or spouse	Yes	446 (78.8)	204 (80.3)	242 (77.8)			0.665
	No	63 (11.1)	25 (9.8)	38 (12.2)			
	Not applicable	57 (10.1)	25 (9.8)	32 (10.3)			
Disclosed HIV status to family members	Yes	349 (61.7)	166 (65.4)	183 (58.7)			0.178
	No	212 (37.5)	87 (34.4)	125 (40.1)			
	Not applicable	5 (0.9)	1 (0.4)	4 (1.3)			
Disclosed HIV status to the public	Yes	12 (2.1)	5 (1.9)	7 (2.2)			0.965
	No	513 (90.6)	231 (90.4)	282 (90.4)			
	Not applicable	41 (7.2)	18 (7.1)	23 (7.4)			
Get useful advice about important things in life	As much as I would like	460 (81.3)	216 (85.0)	244 (78.2)			0.022
	Less than I would like	79 (13.9)	33 (12.9)	46 (14.7)			
	Much less than I would like	11 (1.9)	1 (0.4)	10 (3.2)			
	Never	16 (2.8)	4 (1.6)	12 (3.9)			
Get financial help during emergency	As much as I would like	337 (59.5)	162 (63.8)	175 (56.1)			0.066
	Less than I would like	92 (16.3)	40 (15.8)	52 (16.7)			
	Much less than I would like	44 (7.8)	12 (4.7)	32 (10.3)			
	Never	93 (16.4)	40 (15.8)	53 (16.9)			
Get transportation help when needed	As much as I would like	357 (63.1)	169 (66.5)	188 (60.3)			0.19
	Less than I would like	81 (14.3)	38 (14.9)	43 (13.8)			
	Much less than I would like	45 (7.9)	15 (5.9)	30 (9.6)			
	Never	83 (14.7)	32 (12.6)	51 (16.4)			
Get general help when sick	As much as I would like	456 (80.6)	212 (83.5)	244 (78.2)			0.437
	Less than I would like	67 (11.8)	27 (10.6)	40 (12.8)			
	Much less than I would like	18 (3.2)	6 (2.4)	12 (3.9)			
	Never	25 (4.4)	9 (3.5)	16 (5.2)			

ART adherence

In this study non-adherence was defined as missing to take current ART or missing to take ART dose in the past 30 days. Among all the study patients 371 (n = 566; 65.6%); 164 (n = 254; 64.6%) on NVP and 207 (n = 312; 66.3%) on EFV reported non-adherence in the last 30 days (Fig. 1).

Efavirenz and Nevirapine plasma concentration

Among the patients on nevirapine based ART regimen, the majority (54.3%) had plasma levels of > 6000 ng/ml considered levels for durable viral suppression. There were 80 (31.5%) patients with NVP levels between 3400 to 6000ng/ml considered levels for viral mutant selection windows and the least 36 (14.2%) who had NVP plasma concentration of < 3400 ng/ml considered levels for poor viral suppression ($p < 0.05$). For patients on efavirenz based ART regimen, the majority (63.8%) had plasma concentrations between 1000 to 4000ng/ml considered levels for viral mutant selection windows with some 14(4.5%) had plasma concentrations of < 1000 ng/ml considered levels for poor viral suppression window ($p < 0.05$).

Relationship between HIV related stigma, disclosure and social support and ART adherence

HIV stigma, disclosure and social support related factors influence the drug plasma level by affecting drug adherence. The study first assessed the relationship between social physiological status variables with ART drug adherence and only those factors found significant were then evaluated against drug plasma level. Among these factors included, gender, age, substance abuse, age of sexual debut, number of sexual life partners. Among HIV stigma related factors assessed included; feeling guilty for being HIV positive, hiding HIV status from others and feeling certain to tell primary sexual partner about HIV status. HIV disclose related factors included being able to disclose HIV status to anyone and disclosing the HIV status to family members. Among HIV social support related factors assessed included; getting useful advice about important things in life, getting chance to talk to someone about work or household problems, getting love and affection, being helped with household duties, getting financial and transportation help. Nutritional related factors included: Regular access to staple food, regular uptake of porridge, access to food supplements, Food intake in the last 5–10 days, presence of wasting and feeding syndrome risk (Table 2).

Table 2. Relationship between HIV stigma, disclosure and social support and ART drug adherence

Variable	FISHER'S EXACT TEST	
	ART drug Adherence	
	Nevirapine <i>P value</i>	Efavirenz <i>P value</i>
Socio-demographic variables		
Gender	0.318	0.253
Age	0.393	0.129
Marital status	0.06	0.368
Occupation	0.952	0.565
Religion	0.785	0.689
Education	0.611	0.124
Vacational schooling	0.482	0.209
Living with partner	0.363	0.871
Had more than one partner	0.97	0.533
Previous partner died	0.919	0.953
Smoking	0.725	0.798
Alcohol use number of times	0.011	0.011
Age of sexual debut	0.028	0.024
Number of sexual life partners	0.0001	0.0001
HIV stigma related factors		
Difficult to tell others about my HIV infection	0.234	0.281
Being HIV positive makes me feel immoral	0.260	0.005
Being HIV positive makes me feel guilty	0.035	0.314
Being HIV positive makes me feel ashamed	0.570	0.794
Being HIV positive makes me feel it worthless	0.750	0.344
Being HIV positive makes me feel it is my own fault	0.111	0.318
Hide HIV status from others	0.005	0.605
Feel certain to tell primary sexual partner being HIV positive	0.0001	0.0001
HIV disclosure related factors		
Disclose HIV status to anyone	0.332	0.033
Disclosed HIV status to partner or spouse	0.197	0.578
Disclosed HIV status to family members	0.570	0.730
Disclosed HIV status to friends	0.908	0.383
Disclosed HIV status to neighbor	0.306	0.202
Disclosed HIV status to employers	0.217	0.579
Disclosed HIV status to religious leaders	0.362	0.582
Disclosed HIV status to the public	0.748	0.331
Number disclosed about HIV status in the family	0.185	0.055
HIV social support		
Get useful advice about important things in life	0.022	0.005
Get chance to talk to someone about work or household problems	0.005	0.001
Get chance to talk to someone about personal or family	0.071	0.002
I have people who cares about what happens to me	0.256	0.038
I get love and affection	0.0001	0.008
Help with household duties	0.007	0.001
Get financial help during emergency	0.005	0.045
Get transportation help when needed	0.001	0.014
Get general help when sick	0.138	0.009

Variation in efavirenz and nevirapine plasma level HIV stigma, disclosure and social support related variables

Table 3 summarizes the variation in the median NVP and EFV plasma concentration and socio-demographic, sexual behavior, HIV stigma and disclosure characteristic. Patients who disclosed their HIV status to their employer had higher median (IQR) EFV plasma concentration (3157, IQR = 2001–5976 ng/mL) than those that did not (2173.5, IQR = 1655.5–3208.5 ng/mL; $p = 0.041$). Patients who did not disclose their HIV status to religious leaders had higher median (IQR) EFV plasma concentration (2821.5, IQR = 1945–5270 ng/mL) than those who did (1998.5, IQR = 1548–2520 ng/mL; $p = 0.0031$). Further, patients who disclosed their HIV status to the public had higher median (IQR) EFV plasma concentration (3097, IQR = 2872–5976 ng/mL) as compared to patients who did not (1965, IQR = 1639–2763 ng/mL; $p = 0.0117$).

Table 3. Variation in median efavirenz and nevirapine plasma concentration and HIV stigma, disclosure and social support related variables

Variable	NEVIRAPINE (N = 254)				EFAVIRENZ (N = 312)			
	n	Median	(IQR)	P	n	Median	(IQR)	P
Age group (Years)								
20-30	25	6034	4448 7817		41	2961	1679 4603	
31-40	84	6207	4558 8946.5	0.667	126	2698.5	1918 5976	0.476
41-50	106	6368	4599 9784		96	2685.5	1930.5 4282.5	
>51	39	6011	4518 8843		49	2754	1833 4074	
Gender								
Male	91	5917	4449 8638	0.387	133	2747	1918 5336	0.728
Female	163	6364	4558 9293		179	2712	1868 4647	
Vacational schooling								
Yes	111	6699	5140 9906	0.031	146	2645.5	1917 4713	0.423
No	143	5773	4117 8729		166	2905	1868 5492	
Alcohol use number of times								
Never	204	6351	4407 9194		258	2636	1857 4744	
1 time	33	6180	5128 8573	0.758	45	3093	2068 5787	0.373
≥ 2 times	17	5773	4935 8034		9	2747	2086 5988	
Being HIV positive makes me feel guilty								
Agree	81	5557	4247 7633	0.016	108	2645.5	1895 5171.5	0.927
Disagree	173	6511	4607 9863		204	2854	1869 4839.5	
Being HIV positive makes me feel it worthless								
Agree	55	5243	3975 7311	0.054	82	2756	1951 4319	0.837
Disagree	199	6511	4599 9755		230	2720.5	1838 5204	
Disclosed HIV status to anyone to partner or spouse								
Yes	204	6402.5	4564.5 9180.5		242	2759.5	1886 5204	
No	25	4853	3450 6202	0.036	38	2991	1918 5336	0.565
Not applicable	25	6273	4577 9909		32	2556	1750 3488	
Disclosed HIV status to anyone to family members								
Yes	166	5967.5	4444 7966		183	2592	1917 5044	
No	87	6868	4951 10635	0.064	125	2867	1870 4911	0.312
Not applicable	1	8034	8034 8034		4	1699.5	456.5 3118.5	
Disclosed HIV status to anyone to neighbor								
Yes	13	5239	3631 7009		22	3079	1917 7572	
No	234	6237.5	4558 9095	0.210	280	2739.5	1902 4837	0.088
Not applicable	7	7966	6372 9909		10	2027.5	857 2961	
Disclosed HIV status to anyone to religious leaders								
Yes	18	4479	2960 7009		26	2440	1633 5909	
No	222	6317	4607 9293	0.055	264	2821.5	1945 5270	0.003
Not applicable	14	6371.5	4211 8034		22	1998.5	1548 2520	
Disclosed HIV status to anyone to public								
Yes	5	5736	5239 7009		7	3097	2872 5976	
No	231	6202	4503 9163	0.869	282	2766.5	1918 5139	0.012
Not applicable	18	6595.5	4558 8034		23	1965	1639 2763	
Get financial help during emergency								
As much as I would like	162	6365.5	4558 8964		175	2836	1918 4911	
Less than I would like	40	5468.5	4275 8191.5	0.492	52	2309.5	1789.5 5038	0.797
Much less than I would like	12	7275.5	6056.5 9583		32	2747.5	1615.5 8797.5	
Never	40	5710.5	4046 9867.5		53	2872	2043 4241	
Get transportation help when needed								
As much as I would like	169	6538	4571 9198		188	2821.5	1895 5223.5	
Less than I would like	38	5527.5	4336 8382	0.550	43	2462	1818 4872	0.917
Much less than I would like	15	6202	4180 6868		30	2670	1679 6875	
Never	32	5655.5	3955.5 8750		51	2786	1942 3875	
Get general help when sick								
As much as I would like	212	6351	4448.5 9129		244	2796.5	1895 4977.5	
Less than I would like	27	5911	4990 9411	0.970	40	2569	1999.5 5589.5	0.534
Much less than I would like	6	7039	5729 8405		12	2447.5	911 4693	
Never	9	5692	5457 7009		16	2931.5	1613.5 4168	

Patients with higher median (IQR) EFV plasma concentration were those who did not feel guilty for being HIV positive (6511, IQR = 4607–9863 ng/mL) as compared to patients who felt guilty (5557, IQR = 4247–7633 ng/mL; $p = 0.0163$). Patients who disclosed their HIV status to their spouse (6402.5, IQR = 4564.5–9180.5 ng/mL) had higher median (IQR) NVP plasma concentration than those who did not (4853, IQR = 3450–6202 ng/mL; $p = 0.0362$).

Factors associated with drug plasma concentration

Stigma

In multivariate linear regression analysis, feeling guilty for being HIV positive (adjusted $\beta = 954$, 95% CI = 192.7 to 2156.6; $p = 0.014$) or feeling worthless for being HIV positive (adjusted $\beta = 852$, 95% CI = 64.3 to 1639.7; $p = 0.034$) were independent factors associated with NVP plasma concentrations. For patients on EFV, being certain of telling the primary

sexual partner about HIV positive status was associated with increased EFV plasma levels (adjusted β 363, 95% CI, 97.9 to 628.1; $p = 0.007$) (Table 4).

Table 4. Regression analysis between NVP and EFV plasma concentrations and HIV stigma variables

Variable	NEVIRAPINE (N = 254)			EFAVIRENZ (N = 312)		
	Unadjusted β	(95% CI)	<i>p</i> value	Unadjusted β	(95% CI)	<i>p</i> value
Age	-14	-56.2 28.2	0.307	-13.7	-38.7 11.4	0.284
Gender	447	-545.5 1439.5	0.376	-35	-536.5 466.5	0.891
Vacational schooling	-926	-1753.2 -98.8	0.028	276	-262.4 814.4	0.314
Alcohol use number of times	-198	-680.7 284.7	0.42	330	-534.4 1194.4	0.453
Age of sexual debut	-364	-1385.8 657.8	0.484	54	-459.7 567.7	0.836
Number of sexual life partners	-600	-1285.7 85.7	0.086	-557	-918.0 -196.0	0.003
Number of sexual acts in the past 3 months	-46.5	-748.9 655.9	0.896	-106	-648.9 436.9	0.701
Difficult to tell others about my HIV infection	141	-958.8 1240.8	0.801	-126	-703.9 451.9	0.668
Being HIV positive makes me feel guilty	954	26.7 1881.3	0.044	210	-281.3 701.3	0.401
Being HIV positive makes me feel it worthless	1268	379.4 2156.6	0.005	-33	-744.7 678.7	0.927
Feel certain to tell primary sexual partner being HIV positive	372	-453.2 1197.2	0.376	426	24.3 827.7	0.038
Disclose HIV status to anyone	-539	-1578.8 500.8	0.308	983	-1058.0 3024.0	0.344
Disclosed HIV status to anyone to family members	1051.5	-541.5 2644.5	0.195	134	-381.8 649.8	0.61
Disclosed HIV status to anyone to neighbor	1675	137.5 3212.5	0.033	-445	-1441.0 551.0	0.38
Disclosed HIV status to anyone to employers	-112	-1203.3 979.3	0.84	-489	-1037.2 59.2	0.08
Disclosed HIV status to anyone to religious leaders	1609	-98.7 3316.7	0.065	-410	-907.9 87.9	0.106
Get useful advice about important things in life	-539	-1778.4 1303.7	0.762	-134.3	-483.8 215.1	0.45
Get financial help during emergency	-124.7	-541.9 292.6	0.557	18.7	-189.8 227.1	0.86
Get transportation help when needed	-300	-512.1 -87.9	0.006	-5	-177.6 167.6	0.955
Get general help when sick	-217	-599.7 165.7	0.265	-158	-562.3 246.3	0.442

Variable	NEVIRAPINE (N = 254)			EFAVIRENZ (N = 312)		
	Adjusted β	(95% CI)	<i>p</i> value	Adjusted β	(95% CI)	<i>p</i> value
Age	0.421	-71.7 72.5	0.991	-15.5	-52.5 21.6	0.412
Gender	172	-1010.5 1354.5	0.775	-40.4	-832.7 751.9	0.92
Vacational schooling	-1029	2068.4 10.4	0.042	306.2	-283.9 896.3	0.308
Alcohol use number of times	-162.5	-811 486	0.622	398	-431.2 1227.2	0.346
Age of sexual debut	-1008.1	-2745.4 729.1	0.254	563.5	-424.6 1551.6	0.263
Number of sexual life partners	-988	-2156.8 180.8	0.097	-845.7	-1315.0 -376.4	0.0001
Number of sexual acts in the past 3 months	-2180.8	-5358.2 996.6	0.178	487.3	-3224.2 4198.8	0.796
Difficult to tell others about my HIV infection	-528.5	-1633.9 576.9	0.347	-177	-1021.3 667.3	0.68
Being HIV positive makes me feel guilty	954	192.7 1715.3	0.014	347.7	-153.4 848.7	0.173
Being HIV positive makes me feel it worthless	852	64.3 1639.7	0.034	-143.3	-759.2 472.5	0.647
Feel certain to tell primary sexual partner being HIV positive	341.5	-1357.0 2040.0	0.692	363	97.9 628.1	0.007
Disclose HIV status to anyone	-1042.9	-2597.4 511.6	0.188	1342	1653.6 4337.6	0.379
Disclosed HIV status to anyone to family members	812.9	-483.3 2109.1	0.218	245	-365.8 855.8	0.431
Disclosed HIV status to anyone to neighbor	1731	376.0 3086.0	0.012	-251	-1714.1 1212.1	0.736
Disclosed HIV status to anyone to employers	-393.5	-1586.1 799.1	0.516	-505	-1410.3 400.3	0.273
Disclosed HIV status to anyone to religious leaders	241.6	-1675.6 2158.7	0.804	29	-1120.3 1178.3	0.96
Get useful advice about important things in life	-112.7	-1430.0 1204.6	0.866	16.4	-400.5 433.4	0.938
Help with household duties	-315.2	-1460.0 829.6	0.588	-226.4	-556.1 103.4	0.178
Get financial help during emergency	779.3	-291.9 1850.6	0.153	245.0	-304.7 794.7	0.381
Get transportation help when needed	-1143.3	-1914.3 -372.4	0.004	-6.6	-377.8 364.7	0.972
Get general help when sick	212.3	-560.5 985.1	0.589	74.1	-478.3 626.5	0.792

Disclosure

In multivariate linear regression analysis, disclosing patient's HIV status to neighbors (adjusted $\beta = 1731$, 95% CI = 376 to 3086; $p = 0.012$) was associated with increased NVP plasma concentrations. None of the HIV disclosure related factors were associated with EFV plasma concentrations (Table 4).

Social support

In multivariate linear regression analysis getting transportation to hospital whenever needed (adjusted $\beta = -1143.3$, 95% CI = -1914.3 to -372.4; $p = 0.004$) was associated with lower NVP plasma concentrations. None of the HIV social support related factors were found associated with EFV plasma concentrations (Table 4).

Discussion

Every blueprint and policies geared towards individualization of ART treatment aimed at prolonging life of HIV patients contributes significantly to the components of HIV treatment programs in many countries including Kenya. The recommendation by WHO requiring test and treat of all HIV positive patients regardless of their CD4 or viral load [19], must also appreciate that optimal ART outcomes requires an in-depth understanding of the individual's variation in response to ART, both efficacy and toxicity. ART treatment outcomes are not only influenced by patients pharmacogenetical and pharmacoeconomic factors [20], social psychological (defined as human behavior as a result of the relation between mental state and social situation) well-being of patients is equally important. Stigma, disclosure and social support are social psychological - mental representations are important influence of our interactions with others and environment. This is among the first study to evaluate the influence of HIV stigma (a mark of disgrace, discounting, discrediting and discriminating associated with HIV infection and ARV use) [21], HIV disclosure (action of making new or secret of being HIV positive known) and HIV social support (the perception and actuality that one is cared for or having assistance available from other people) on the steady-state plasma concentrations of nevirapine and efavirenz among HIV patients receiving treatment in Nairobi Kenya.

HIV stigma, disclosure and availability of social support are key determinant to patient's behavior and influences adherence to HIV care, treatment and prevention. Previously in Kenya, involvement in community support networks considerably enriched adherence and treatment outcome [22]. Further, patients vigorously partaking in community support networks inclined towards attaining peak NVP plasma concentration early hours post-dosing, which were markedly higher than seen in patients not actively involved in community support networks. Countless studies have interconnected social support to better medication adherence and better clinical outcomes [23].

HIV associated stigma related factors such as feeling guilty, worthless for being HIV positive were associated with higher median NVP plasma levels. For patients on EFV based regimen, those who were certain to reveal their HIV status to their primary sexual partner had better ART adherence accompanied by higher median EFV plasma levels. Stigma and discrimination remain the paramount challenge confronted by People Living with HIV/AIDS [24]. Although data are skewed on the association between HIV stigma and NNRTI plasma level, stigma and discrimination negatively affect people living with HIV [25]. HIV-related stigma is wide-ranging and worldwide social phenomenon that exhibits within multiple social spheres, including healthcare encompassing denial of care or treatment, HIV testing without consent, confidentiality breaches, negative attitudes and humiliating practices by health workers [26]. Studies have shown an association between HIV stigma with poorer physical and mental health outcomes [27]. Stigma has also been linked with secondary health-related factors including seeking healthcare and adherence to antiretroviral therapy, and access to and usage of health and social services [27, 28]. Inevitably, these negative outcomes of stigma are bound to affect the overall treatment outcomes in terms of therapeutic monitoring.

HIV status disclosure in our study was associated with ART adherence which was marked by higher median NVP and EFV plasma concentration regardless whether the disclosure was to a spouse, family member, religious leaders and employers. In Thailand, Sirikum *et al.*, [29] reported no significant difference in the median ART adherence by pill count, CD4 count, or HIV viral load between HIV patient disclosed their status compared to those who did not. Studies have shown HIV disclosure to have two possible treatment outcomes [30]. On one hand; HIV status disclosure to sexual partners is a vital prevention target underlined by both WHO and the Centers for Disease Control and Prevention (CDC) [31], at an individual level and to the general public, HIV disclosure is accompanied by numeral benefits [29]. HIV infection disclosure to sexual partners is associated with less anxiety and increased social support especially among women [30, 31]. Further, HIV status disclosure is accompanied by improved access to HIV prevention and treatment programs, increased opportunities for risk reduction and increased opportunities to plan for the future. Disclosure of HIV status also expands the awareness of HIV risk to untested partners leading to better acceptance and utilization of voluntary HIV testing and counselling and changes in HIV risk behaviors [30, 31]. In addition, disclosure of HIV status to

sexual partners empowers couples to make educated reproductive health choices that may eventually lower the number of unintended pregnancies among HIV-positive women [30]. Along with these benefits, however, there are a number of potential risks from disclosure for HIV-infected women, including loss of economic support, blame, abandonment, physical and emotional abuse, discrimination and disruption of family relationships [30, 31]. These risks may lead women to choose not to share their HIV test results with their friends, family and sexual partners. This, in turn, leads to lost opportunities for the prevention of new infections and for the ability of patients especially women to access appropriate treatment, care and support services where they are available [30, 31].

In our study, patients who had adequate social support such as getting useful advice about important things in life, having a chance to talk to someone about work, household, personal or family problems, getting love and affection had higher median NVP and EFZ plasma concentration. In South Africa, Brittain *et al.*, [32] showed correlation between social support and stigma influencing whether or not the development of depressive symptoms. The importance of community support networks in enhancing social relationships demystifying HIV-associated stigma is well documented [33, 34]. Evidence shows the positive effects of social support and protection on other HIV related outcomes, such as sexual risk behaviors [35, 36], mental health distress and family relationships [37, 38]. Growing evidence of associations between social protection and HIV-risk reduction [39] is reflected in a number of policy documents by UNICEF, UNAIDS and PEPFAR-USAID that focus on pediatric and adolescent HIV-prevention [40, 41].

Conclusions

Some of the important limitation worth mentioning in this study included. First, the use of NVP-based ART regimen in Kenya and other countries, especially developed countries, has been considerably reduced in the recent past, meaning that this study could be relevant to a restricted number of patients. Second, standardized tools for measuring stigma, disclosure and social support were not used in this study limiting the generalizability of this study outcome. Fourth, this was a cross-sectional study, which only permitted the description of the relationship between the three socio-psychological factors and NVP/EFV plasma concentrations and not a causal conclusion. Such outcomes can be confirmed in a longitudinal study.

These limitations notwithstanding, our study, conducted in one of the oldest and largest cosmopolitan treatment centers in Kenya, shows the significant HIV stigma, lack of HIV status disclosure and inadequate social support among the HIV infected patients is still noticeable. Further, HIV stigma, disclosure and social support contributes significantly nevirapine and efavirenz plasma concentrations by influencing ART drug adherence. Integrating socio-psychological support in the individualization of ART treatment could also lead to optimal ART plasma concentration.

Declarations

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Conflicts of interest/Competing interests: None

Ethics approval: Ethical approval for this study was obtained from KEMRI Scientific Review Unit (SERU). The protocol number is SSC No. 2539

Consent to participate: Written informed consent was obtained from all subjects before the study.

Consent for publication: Was granted at the time of consenting

Availability of data and material: All data will be stored at figshare at the moment submitted as electronic data

Code availability: not applicable

Author's Contribution: MON, MO conceived the study. MON collected samples and conducted laboratory analysis. MO, WDB and FAO supervised laboratory analysis. MON analyzed the data and prepared the draft manuscript. MO, WDB and FAO provided guidance and mentorship during the implementation of the study. All authors reviewed and approved the final manuscript.

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Figures

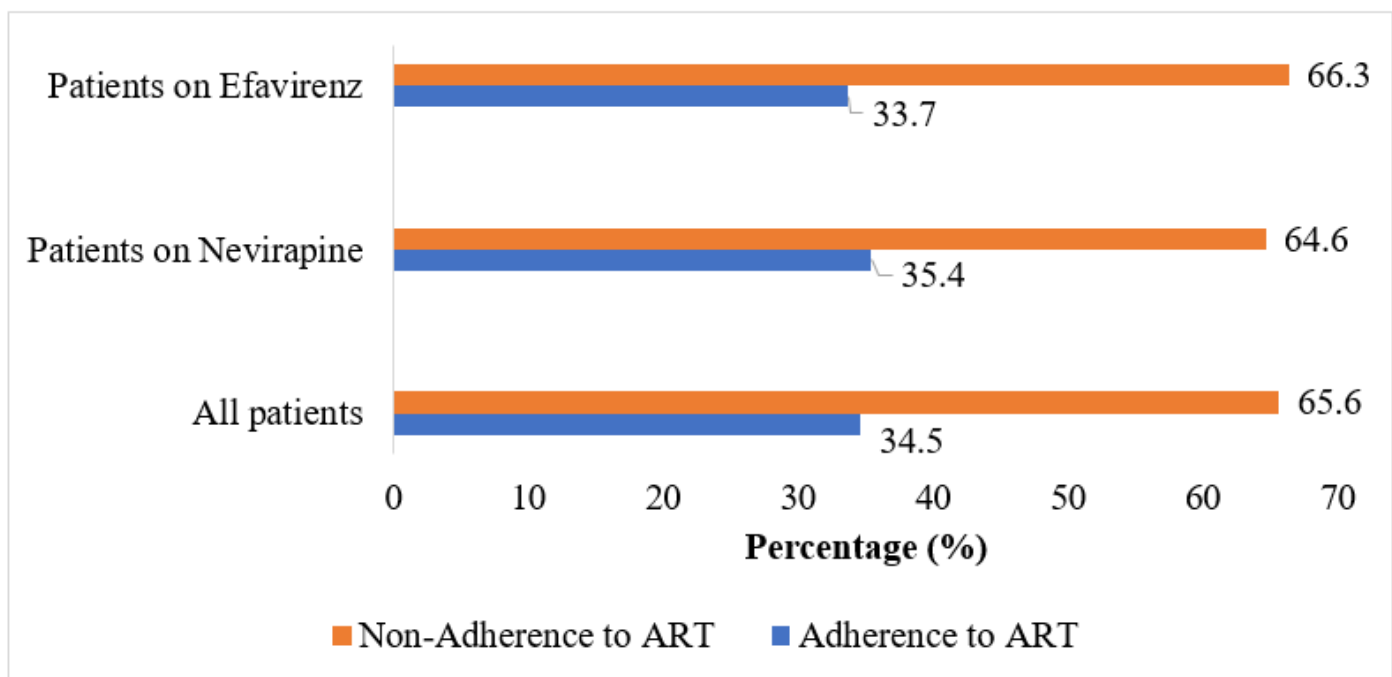


Figure 1

Distribution of patients ART adherences in the past 30 days

Supplementary Files

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- [MusaStigmaData.xlsx](#)