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Socio-Demographic, Nutritional and Adherence as Determinants of Nevirapine Plasma Concentration among HIV-1 Patients from Two Geographically Defined Regions of Kenya

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Abstract
Background: Data are skewed on the role of Socio-demographic, nutritional and adherence related factors on the influence of nevirapine plasma concentrations among Kenyan population. This study rigorously determined these three factors on nevirapine plasma concentrations among HIV patients receiving HIV treatment in two regions known for high prevalence of HIV and long duration of ART uptake.**Methods:** Blood samples were collected from 377 consenting HIV adult patients receiving an NVP-based first-line ART regimen. A detailed sociodemographic questionnaire was administered. NVP plasma concentration was measured by liquid chromatography - tandem mass spectrometry (LC-MS/MS). **Results:** The majority (59.2%) of the patients were female, 72.2% were from western Kenya (predominantly Nilotic speaking community). The patients' mean age was 41.6 (SD ± 11.5) years and the mean duration of ART was 5.1 (SD ± 4.8) years. The median BMI of the patients was 25 kg/m^2 (IQR = 22.2 - 28.7 kg/m^2). The majority 81.2% were receiving 3TC/NVP/TDF ART regimen, 30% had changed their initial ART regimen with 54.4% reporting missing taking current ARVs. Overall NVP plasma levels ranged from 4-44207 ng/mL (median 6213 ng/mL, IQR 3097–8606.5 ng/mL). There were 105 (25.5%) participants with NVP levels of <3100 ng/mL, associated with poor viral suppression. Multivariate linear regression analysis showed region of origin (adjusted β 976, 95% CI, 183.2 to 1768.82; p = 0.016), gender (adjusted β 670, 95% CI, 293.6 to 1634.2; p = 0.047), education level (adjusted β -39.0779, 95% CI, -39.07 to 1085.7; p = 0.068), initial ART regimen type (adjusted β = -548.1, 95% C = -904.2 to -192; p =0.003) and ARV uptake in the past 30 days (adjusted β = -1109, 95% C = -2135 to -83; p =0.034) remained independently associated with NVP plasma levels.**Conclusion:** NVP plasma concentration is highly heterogenous among Kenyan population with a significant proportion of patients reporting levels of <3100 ng/ml, correlated with poor viral suppression. The host pharmacoecologic factors, such as gender, age, weight, education level, region of origin (ethnicity), ART regimen type and adherence, are key in influencing NVP plasma concentration. Taking these factors into consideration, HIV treatment may be personalized to achieve optimal treatment success.
Keywords: Nevirapine plasma concentration, host pharmacoecologic factors, HIV-1 patients in Kenya
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Background

Globally, the introduction of antiretroviral therapy (ART) as treatment for HIV infections has greatly reduced mortality and morbidity among patients living with HIV (UNAIDS, 2020). Kenya is steadily on the track for scale up of ART uptake in line with the 2015 World Health Organization recommendations requiring immediate initiate ART treatment to people testing HIV positive regardless of their CD4 or viral load (UNAIDS, 2016). By the end of 2019, about 74% adults and 73% children in Kenya needing ART were receiving ART treatment (UNAIDS, 2020). A remarkable proportion of these patients (68%) were virally suppressed (UNAIDS, 2020). At the time of the 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], stavudine [d4T], tenofovir [TDF] or lamivudine [3TC]), plus one non-nucleoside reverse transcriptase inhibitor (NNRTI): either nevirapine (NVP) or efavirenz (EFV) (NASCOP, 2016).

Nevirapine has been widely used in Kenya just like in many developing countries. Efficacy, availability, low cost and use in prevention of vertical HIV transmission are the key reasons for this choice (WHO, 2016). Unfortunately, NVP is associated with a higher incidence of rashes (van Leth et al., 2004), hepatotoxicity (Aizire et al., 2012) and a low genetic barrier to resistance limiting the use of this drug (Clutter et al., 2016). In some countries especially, the developed countries the drug is no longer dispensed. Several factors are pointed out affecting NVP plasma concentration. Pharmacogenetic factors such as the occurrence of single-nucleotide polymorphisms (SNPs) in the P450 2B6 (CYP2B6) and minorly by CYP3A have been extensively documented affecting NVP plasma concentration (Xu et al., 2012). The association between CYP2B6 SNPs and NVP plasma concentration has also been widely published in Kenya (Oluka et al., 2015); including among the population in the current study (Mungiria et al., 2020). Other factors affecting NVP plasma levels identified in other settings

but yet to gain much attention especially among the Kenyan population includes holistic socio-demographic, nutritional and adherence related factors (Bennett et al., 2008; Wang et al., 2011).

Data aimed at individualization of ART treatment in Kenya are key to successful ART treatment programs. This study rigorously evaluated the relationship between socio-demographic, nutritional and adherence related factors with NVP concentrations among HIV-1 patients receiving ART treatment in western and coastal Kenya.

Methods

Design and study population

A cross-sectional study approved by the Kenya Medical Research Institutes' (KEMRI) Scientific Review Unit (SERU) (KEMRI/SERU/CVR/002/3214) and NACOSTI (NACOSTI/P/19/11747/28173) was conducted between August, 2018 and January 2020. Patients recruited in this study were part of an ongoing study designed to establish a cost-effective laboratory method to monitor antiretroviral adherence in HIV-1 infected individuals on treatment in Kenya. The patients recruited in this study were those: (i) HIV-1 infected adults (aged above 18 years), attending the two HIV treatment programs, (ii) willing to voluntarily give written informed consent, (iii) able to read either English or Kiswahili, (iii) be on ARV treatment for 12 months, (iv) be on nevirapine based first line ARV treatment regimen and (v) HIV patients with viral load results at month 12 of treatment. All patients filled in a written informed consent for study participation

Data collection

Detailed description of the population of the study has been described previously (Mungiria et al., 2020). The study recruited 272 patients from Kisumu (western region of Kenya) and 105 patients from Malindi (coastal region of Kenya). An exhaustive structured interview (including demographic data, clinical history, adherence, HIV stigma and medical history) was used to collect patient-related information. From each patient, about 5 ml of intravenous blood was collected into ethylenediaminetetraacetic acid (EDTA)-containing Vacutainers® (BD, US) for determination of NVP plasma concentration measurement using a tandem quadrupole mass spectrometer designed for ultra-high performance: Xevo TQ-S (Waters Corporation, U.S.A) as described by Reddy *et al.* (2016). 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) as previously defined (Gopalan et al., 2017; Mungiria et al., 2020).

Data analysis

Frequencies and percentages were used to present the sociodemographic data. The effect of socio-demographic, nutritional and adherence on NVP plasma concentrations was determined using Kruskal-Wallis test and Dunn's test at $\alpha = 0.05$. Univariate and multivariate linear regression analyses were performed to determine the relationship between NVP plasma concentration and Socio-demographic, nutritional and adherence and other clinical characteristics at 5% significance level. All statistical analyses were performed using STATA v 13 (StataCorp LP, Texas, USA).

Results

Baseline characteristics

The results from the all the 377 patients were assessed, of whom 272 (72.2%) were from Kisumu county (western region of Kenya), 223 (59.2%) were female and 114 (30.2%) had a HIV viral load of >1000 copies/mL. The median age of the patients was 41 years (IQR = 34–49 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). The median BMI of the patients was 25 kg/m^2 (IQR = 22.2 - 28.7 kg/m^2). There were 988(26%) of the patients whose staple food stuff was protein and carbohydrates with 264(70%) reporting lacking staple foods during the study. At the time of the study, there were 169 (44.8%) patients taking lamivudine, nevirapine, tenofovir regimen, with 205 (54.4%) reporting missing taking current ART at least once (Table 1).

Table 1. Summary of patient demographics and clinical characteristics of patients

Variables	Total (N = 377)	
Region - Kisumu, n (%)	272	72.2
Female, n (%)	223	59.2
Age (years), Median (IQR)	41	(34 - 49)
HIV-RNA <1000copies/mL copies/mL, n (%)	263	69.8
Time to HIVclinic (Minutes) Median (IQR)	60	(40 - 90)
Duration with HIV (Years), Median (IQR)	5	(1 - 11)
Age of sexual debut (Years), Median (IQR)	18	(16 - 20)
Duration post ART initiation (Years), Median (IQR)	3	(1 - 8)
BMI (kg/m2), median (IQR)	25	22.2 - 28.7
Staple food stuff (Proteins/Carbohydrates) n (%)	98	26
Missed staple food n (%)	264	70
Porridge consumption (≥ 2 times) n (%)	147	39
Initial ARV Type		
Lamivudine, Nevirapine, Stavudine	131	34.7
Lamivudine, Nevirapine, Zidovudine	134	35.6
Lamivudine, Nevirapine, Tenofovir	112	29.7
Changed ARV, yes n (%)	113	30
Current ARV Type		
Lamivudine, Nevirapine, Stavudine	83	22
Lamivudine, Nevirapine, Zidovudine	125	23.2
Lamivudine, Nevirapine, Tenofovir	169	44.8
Missed taking current ART n (%)	205	54.4
76 - 100 % uptake of current ART n (%)	345	91.5
Missed taking ART n (%)	27	7.2

NVP plasma concentration

The steady-state NVP plasma concentrations ranged from 4 to 44,207 ng/mL (median 5179, IQR 2557–7453 ng/mL) varying widely among patients. There were 96 (n = 377, 25.5%) patients with NVP concentration <3100 ng/mL and 26 (n = 377, 6.9%) with NVP concentration of 3100-4300 ng/mL, with the majority, 255 (n = 377, 67.6%), of the patients having an NVP concentration >4300 ng/mL. The steady-state plasma nevirapine concentrations was tested for normality by the Shapiro- Wilk test, and subsequently $\log_{10}$-transformed due to lack of normality (Shapiro- Wilk test = 0.86194; v = 36.048; p = 0.000001).

Linear regression model

Socio-demographic characteristics

In the final linear regression model, sociodemographic factors significantly associated with a higher NVP concentration included region of origin (adjusted β 976, 95% CI, 183.2 to 1768.82; p = 0.016) and gender (adjusted β 670, 95% CI, 293.6 to 1634.2; p = 0.047). Education level on the other hand was associated with a lower NVP were education level (adjusted β -39.0779, 95% CI, -39.07 to 1085.7; p = 0.068, (Table 2)

Table 2. Univariate and multivariable regression analyses of Socio-demographic factors associated with NVP plasma concentrations.

Variable	Bivariate				Multivariate			
	Unadjusted β	(95% CI)		P-value	Adjusted β	(95% CI)		P-value
Age	282.5	-86.9	651.9	0.133	393	-168.7	954.0	0.17
Gender	612	-329.1	1553.1	0.089	670	293.6	1634.2	0.047
Religion	-769	-3173.9	1635.9	0.53	-648	-2731.8	1435.1	0.541
Education	565	-18.4	1148.4	0.058	502	60.6	943.4	0.026
Ever been married	60	-1187.6	1307.6	0.925	-335	-2299.5	1628.9	0.737
Currently Married	250	-935.6	1435.6	0.679	251	-698.1	1200.7	0.603
Region	670	-218.2	1558.2	0.139	976	183.2	1768.8	0.016
Ethnicity	-412.5	-862.9	37.9	0.073	-333	-845	179	0.202
Alcohol use	-18.5	-1145.2	1108.2	0.974	25.6	-953.2	1004.4	0.959
Smoking	-97	-3126.2	2932.2	0.95	127.1	-2167.4	2421.6	0.913

Nutritional factors

None of the nutritional related factors were found associated with NVP plasma concentration (Table 3).

Table 3. Univariate and multivariable regression analyses of nutritional factors associated with NVP plasma concentrations.

Variable	Bivariate				Multivariate			
	Unadjusted β	(95% CI)		P-value	Adjusted β	(95% CI)		P-value
Body Mass Index (Kg/M2)	-51.5	-358	255	0.741	-92.2	-589.1	404.7	0.715
Types of stable food stuff	-132	-428.3	164.3	0.382	-120.6	-319.6	78.4	0.234
Access to staple food	1958	-2139.8	6055.8	0.348	1826.6	-1683.2	5336.4	0.307
Missed staple food	435	-141.1	1011.1	0.138	351	-507.1	1209.1	0.422
No of times missed staple food	-125	-1512.8	1262.8	0.86	-441.1	-1646.9	764.6	0.472
Meal preparation	290	-659.6	1239.6	0.549	196.7	-436.4	829.7	0.542
Porridge consumption	49.5	-491.2	590.2	0.857	-40.4	-677.5	596.6	0.901

ART treatment and adherence related factors

Table 4 describes linear *regression analysis* estimating the relationships between NVP and plasma levels and ART history and adherence factors. In multivariate analysis, initial ART regimen type (adjusted β = -548.1, 95% C = -904.2 to -192; p = 0.003) and ARV uptake in the past 30 days (adjusted β = -1109, 95% C = -2135 to -83; p = 0.034) remained independently associated with NVP plasma levels.

Table 4. Univariate and multivariable regression analyses of ART treatment and adherence related factors associated with NVP plasma concentrations.

Variable	Bivariate				Multivariate			
	Unadjusted β	(95% CI)		P-value	Adjusted β	(95% CI)		P-value
Time taken to ARV clinic (Minutes)	3.1	-6.4	12.5	0.528	191.4	-1175.4	1558.2	0.783
Fare to ARV clinic (Ksh)	121	-849.2	1091.2	0.806	-1084.5	-3149.4	980.5	0.302
Hospital Admission	-1279	-2622.7	64.7	0.062	1100.6	-3033.7	1294.9	0.43
No of times missed HIV medical visits	602.5	-74.3	1279.3	0.081	393.3	-415.5	1131.3	0.363
Missed ART schedulled visit	111	-934.6	1156.6	0.835	605.4	-854.1	1526.8	0.579
Duration post ART initiation (Years)	-39	-615.6	537.6	0.894	435.7	-1429.6	2300.9	0.646
Initial ARV Type	-506.8	-778.9	-234.6	0.0001	-548.1	-904.2	-192	0.003
Changed ARV	-1238	-1895.9	-580.1	0.0001	-159.6	-1233.7	914.6	0.77
Current ARV Type	87	-894.1	1068.1	0.862	523.5	-651.3	1698.2	0.381
Missed taking current ART	-986	-1661.1	-310.9	0.004	-192.9	-1173.5	787.7	0.304
Percent uptake of current ART (%)	-43.8	-81.5	-6.1	0.023	68.5	-2295.2	2432.3	0.955
Missed taking past ART	-906	-1861.1	49.1	0.063	-602.4	-3362.2	2157.3	0.668
Missed ARV uptake 4 to 14 days	-441	-1262.4	380.4	0.292	67	-1097.0	1231.0	0.91
Missed ARV uptake ≥ 14 days	-447	-1476.3	582.3	0.394	-613.5	-1954.3	727.3	0.369
ARV dose missed yesterday	-2959	-4795.1	-1122.9	0.002	-2097.5	-4825.7	630.7	0.131
ARV dose missed in the past 2 days	-1457.5	-4089.8	1174.8	0.277	1183.5	-936.5	3303.5	0.273
ARV dose missed in the past 3 days	-2517.5	-4070.9	-964.1	0.002	-2059.5	-4696.9	577.9	0.126
ARV uptake in past 30 days	-822	-1625.5	-18.5	0.045	-1109	-2135	-83	0.034
ARV dose missed in the past 30 days	-179	-1048.4	690.4	0.686	-176	-939.9	587.9	0.651

Discussion

Efforts contributing to the personalization of ART treatment aimed at prolonging life of persons living with HIV marks huge component of HIV treatment programs in many countries. The recommendation by WHO requiring immediate initiate ART treatment to people testing HIV positive regardless of their CD4 or viral load (UNAIDS, 2016), must also take cognizant of the fact that optimal ART outcomes inevitably requires an understanding of the individual variation in response to ART, both efficacy and toxicity. ART treatment outcomes are influenced in part by host pharmacoecologic factors (Phillips and Mallal, 2009). The pharmacoecologic factors include factors relating to lifestyle and adherence of the patient, drug interactions or pregnancy (Pavlos and Phillips, 2012). Patients demographic factors such as age, gender (Wyen *et al*., 2008; Swaminathan et al., 2011), nutritional status such as body weight, growth rate (Schipani et al., 2011) are also shown to influence the treatment outcomes attributed (Gopalan et al., 2017). This study evaluated the influence of socio- demographic factors (such as age, sex, education level), nutritional status and ARV treatment and adherence on the steady-state plasma concentrations of nevirapine among HIV patients receiving treatment in two regions of Kenya known for high prevalence of HIV as well as uptake of ART treatment in Kenya.

We reported wide interindividual variability in NVP plasma levels ranging from 4ng/mL to 44,207 ng/mL (median 5179 ng/mL, IQR 2557–7453 ng/mL). This range is far broader than those reported in other studies (Oluka et al., 2015; Giacomelli et al., 2018; Mazanderani et al., 2019). There were 255(67.6%) patients with NVP plasma of 3000 to 8000 ng/mL (la Porte et al., 2006) considered within therapeutic range. Further, there were 25.5% patients who had NVP plasma levels of <3100 ng/ml, correlated with poor viral suppression (la Porte et al., 2006). Previous studies in Kenya and in other countries such as Italy have reported fewer cases of persons with NVP plasma level of levels of <3100 ng/ml (Oluka et al., 2015; Giacomell et al., 2018).

Region of origin contributed significantly to NVP plasma concentration with the patients from coastal

Kenya region having higher median NVP plasma concentration than those from Western Kenya region. A similar observation was made among the Bantu-related communities from Serowe/Palapye and Chobe districts, and the San-related communities of the Ghanzi area in Botswana (Tawe *et al*., 2018). Kenya's ethnic groups can be divided into three broad linguistic groups: Bantu (mostly in the Central Kenya), Nilotic (western Kenya) and Cushite (Coastal and Northern Kenya). Although these ethnic groups reside in close proximity to each other, there is wide environmental and cultural diversity between these populations (Kenya National Bureau of Statistics, 2019). Consequently, there exist wide host genetic and environmental diversity which may result in different efficacy and adverse event profiles or treatment outcome between different African populations treated with same ART regimen (Ngaimisi *et al*., 2013). The human cytochrome P450 2B6 enzyme (CYP2B6) plays a pivotal role in the metabolism of different drugs used for HIV life-long therapy (non-nucleoside reverse-transcriptase inhibitors such as efavirenz and nevirapine). CYP2B6 is a highly polymorphic enzyme that affects the therapeutic response including drug interactions in individuals (Hedrich *et al*., 2016). Importantly, African populations show a high degree of variation in the *CYP2B6* gene (Čolić *et al*., 2015).

Males in this study tended to have elevated median NVP plasma concentration than female contrary to several independent studies (Gonzalez et al., 2005; Shiau *et al*., 2014; Giacomell et al., 2018). Generally, the difference in ARV plasma levels by gender has been attributed to the difference in body size and drug clearance between males and females. Although not significant, the older patients had higher median NVP plasma level than younger ones. This is consistent with other studies which have indicated that nevirapine metabolism in younger population is generally more rapid than older population, and that younger population including children require higher doses of nevirapine to achieve therapeutic concentration (Swaminathan *et al*., 2011; Gopalan *et al*., 2017).

The observed association between education level and NVP plasma levels suggests that literacy, formal education and possibly Koranic education may impact favorably on adherence to ART with better treatment outcome (Hegazi et al., 2010).

We did not observe an association with NVP plasma concentration and nutritional related factors such as body mass index, regular uptake of porridge, availability of balanced diet and access to staple food. However, patients with BMI of >30kg/m^2 (obese), accessed balanced diet and regularly consumed porridge tended to have higher NVP plasma concentration. Studies have associated body composition, nutritional status, food security with NVP plasma concentration (Vreeman *et al*., 2014; Bartelink *et al*., (2015). The lack of proper nutrition and/or a diet low in fat are shown to affect ARV absorption, or ARV cellular transport (Lamorde *et al*., 2012).

We observed the importance of initial ART regimen type and ARV uptake in the past 30 days influencing NVP plasma concentration. Access to ART is only one aspect of an effective HIV management programme (Moosa *et al*., 2019). Optimal adherence to ART is essential and early studies reported that ≥95% adherence to ART was required to achieve and maintain viral suppression (Paterson *et al*., 2000). Although recent studies have shown that virologic suppression may still be achieved with < 95% adherence levels, this is dependent on the ART regimen, duration of treatment and previous ART exposure (Talam et al., 2008; Ammassari *et al*., 2016). Furthermore, repeated adherence levels of < 100% and treatment interruptions are associated with an increased risk of both NRTI and NNRTI resistance which form the backbone of current first line ART regimens in Kenya and many other developing nations (Haberer *et al*., 2015; Kimulwo *et al*., 2017). The important ART regimen type and adherence to treatment cannot be overemphasized in achieving HIV treatment success.

Some of the limitation to this study included: First, the use of an NVP-based ART regimen in Kenya and other developed countries has been reduced if not eliminated in the recent past, limiting the generalization of these results. Secondly, this study did not delve deeper into ethnic profiling of study participants and the actual influence of ethnicity to treatment outcome cannot be ruled out. Lastly the cross-sectional nature of this study only permitted the description of the relationship between NVP plasma concentrations the stated pharmacoecologic factors and not a causal conclusion. Such outcomes can be confirmed in a longitudinal study.

Recognizing these limitations, the following can be concluded, NVP plasma concentration is highly heterogenous with a significant proportion of these patients reporting levels of <3100 ng/ml, correlated with poor viral suppression. The host pharmacoecologic factors, such as gender, age, weight, education level, region of origin (ethnicity), ART regimen type and adherence, are key in influencing NVP plasma concentration. Taking these factors into consideration, HIV treatment may be personalized to achieve optimal treatment success

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Declaration of Conflicting Interest
The author(s) declared no competing interests.

Ethics approval

This study was approved by the Kenya Medical Research Institutes' (KEMRI) Scientific Review Unit (SERU) (KEMRI/SERU/CVR/002/3214) and NACOSTI (NACOSTI/P/19/11747/28173). Before recruitment in this study, all patients filled in a written informed consent for study participation

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Informed consent

Written informed consent was obtained from all subjects before the study.

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