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CYP2B6 and *SULT1A1* single nucleotide polymorphism among Ghanaian HIV patients

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Abstract

Background: Nevirapine is used in many developing countries for the management of HIV-1 patients. Despite its usefulness, hypersensitivity reaction is a common complication that accounts for patients defaulting during therapy in Ghana. Genetic variations in drug-metabolising enzymes have been implicated in reported adverse drug reactions observed in patients on nevirapine regimen.

Objective: This study aimed to determine genotypic frequencies of specific *CYP2B6* and *SULT1A1* variants and their association with nevirapine hypersensitivity among persons living with HIV in the Ghanaian population.

Methods: A prospective study was conducted in Korle-Bu Teaching Hospital, a tertiary health facility in Ghana. Clinical data were recorded from the seventy patients' folder, and whole blood was collected for genotyping. Genotypes of *CYP2B6c.983T > C* and *SULT1A1c.638G >* A were obtained using Restriction Fragment Length Polymorphism method.

Results: The mean age of the participants was 38 ± 9.47 years, with the majority 77% being females. For *CYP2B6c.983T > C* genotype frequencies, T/T and T/C were 94.3% and 5.7%, respectively, while for *SULT1A1c.638G > A* genotype frequencies, G/G, G/A, and A/A were 61.4%, 34.3% and 4.3% respectively. The prevalence of *CYP2B6c.983T > C* and *SULT1A1c.638G > A* minor allele was 2.9% and 21.4%, respectively among the study participants.

Conclusion: Extensive metaboliser genotypes for *CYP2B6c.983T > C* and *SULT1A1c.638G >* A were more than the intermediate and poor metaboliser genotype. However, *CYP2B6 983C/C* representing poor metabolisers of CYP2B6c.983T>C were not detected among the study population. Genetic polymorphism of *CYP2B6c.983T > C and SULT1A1c.638G > A* were not associated with nevirapine hypersensitivity.

Keywords: CYP2B6, HIV, Nevirapine, SULT1A1

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INTRODUCTION

The scale-up of anti-retroviral therapy (ART) for HIV patients is one of the most remarkable achievements in public health, leading to a substantial decline in new HIV infections [1]. However, Adverse Drug Reactions (ADR) are a very common complication of ART and a reason for patients defaulting during HIV therapy in many developing countries [2]. Genetic factors are estimated to contribute about 20-95% to the variability in individual drug response and safety [3]. Cytochrome P450 (CYP) and Sulfotransferase (SULT) play dominant roles in the metabolism of some anti-retroviral drugs and their metabolites, respectively [4,5]. The expression and function of these metabolising enzymes are highly variable and, thus, are major contributors to drug or metabolite plasma concentrations and adverse drug reactions [6].

Highly polymorphic *CYP2B6* is a major enzyme involved in the phase I biotransformation of some ART, including nevirapine (NVP) [7]. While the reasons for the ADR of nevirapine are still unclear, increasing evidence suggests that genetic factors have a role in the initiation of the toxic

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responses [8]. Nevirapine has been associated with hypersensitivity reactions characterised by skin rash and hepatotoxicity, culminating in 6 - 15.7% of patients switching therapy in Ghana [9,10]. Approximately 10% of patients treated with nevirapine in clinical trials developed hepatotoxicity; 3.7% of these patients experienced symptomatic elevations of their liver enzymes, with nearly half (46%) of the patients with hepatotoxicity also developing a rash [11]. Single nucleotide polymorphisms (SNPs) within *CYP2B6* genes have been reported to influence NVP metabolism [12,13)]. The *CYP2B6* isozyme which is predominantly expressed in the liver (23) has been associated with reduced catalytic activity and protein stability, resulting in increased NVP plasma levels [14,15]. *CYP2B6c.516G > T* and *CYP2B6c.983T > C* have been associated with NVP-induced hypersensitivity, Steven Johnson Syndrome and toxic epidermal necrolysis in Blacks, Asians and Whites [12,13,16,17]. *CYP2B6c.983 T > C* has a frequency of around 5 - 10% in African populations, with 3.1 - 7.6% among Ghanaians, and this may represent an ethnicity-specific predisposing factor [13,18,19]. However, there is limited data on the association between genotypic frequencies of *CYP2B6c.983T > C* and its association with nevirapine-induced hypersensitivity among HIV patients in Ghana.

Primarily, *CYP2B6* and *CYP3A4* metabolise NVP to 2-hydroxynevirapine (OH-NVP), 3-OH-NVP, 8-OH-NVP, and 12-OH-NVP. However, reactive metabolite, 12-sulphoxynevirapine (12-SUL-NVP) from the SULTs biotransformation of 12-OH-NVP is also known to be a major contributory factor of NVP Hypersensitivity [20,21]. Highly polymorphic sulfotransferase 1A1 (*SULT1A1*) is marked with differences in their variants with significantly reduced enzyme activity [22]. *SULT1A1c.638G > A* polymorphism may cause R213H amino acid change and consequently result in significantly reduced enzyme activity [22]. In vitro analysis shows that the mutagenicity of 12-OH-NVP to induce hypersensitivity is dependent on *SULT1A1* (14). Despite its major role *SULT1A1* in 12-OH-NVP clearance [21], *SULT1A1* has not been investigated as to whether its polymorphism may have a possible impact on developing NVP-hypersensitivity. Little is known regarding genetic risk factors for nevirapine-induced hypersensitivity in sub-Saharan Africa [13]. *CYP2B6 516G > T* and *CYP2B6c.983T > C* have been reported to be significantly associated with an increased risk of developing nevirapine hypersensitivity in Malawian, Mozambique and Ugandans [13,16].

Consequently, the genetic variations among ethnic groups across different regions require that *CYP2B6c.983T > C* and *SULT1A1c.638G> A* polymorphisms and their association with NVP-hypersensitivity should be investigated among the Ghanaian population. We genotyped *CYP2B6c.983T > C* and *SULT1A1c.638G > A* using PCR-RFLP to determine the association of these alleles to NVP-hypersensitivity in Ghanaian HIV-1 infected patients.

MATERIALS AND METHODS

Study population and sites

This prospective cohort study involved seventy nevirapine-naïve HIV-1 patients who started nevirapine-based HIV therapy and were clinically evaluated for at least a year at the Korle-Bu Teaching Hospital, Ghana. Blood samples were tested for alanine and aspartate aminotransferase activity, and DNA was genotyped for *CYP2B6* and *SULT1A1* variants. Inclusion criteria included patients 18 years and above who had NVP as their first exposed ART drugs as part of their treatment at the clinic. The study excluded patients who were co-infected with hepatitis before NVP initiation and patients previously on different ART before switching to NVP-based ART. Participants with elevated serum transaminase levels (>33 U/L for males and > 25 U/L for females) and high CD4+ T-cells (> 350 cells/µL in females and > 400 cells/µL in males) prior to NVP therapy were excluded. Pregnant women and patients presenting with jaundice were also excluded from the study. Socio-demographic data were obtained from hospital records.

HIV-1 patients who developed NVP-induced hypersensitivity after six months of initiating NVP were recruited as cases, while those who were NVP-tolerant as the controls. Hypersensitivity was characterised as NVP-induced skin rash (confirmed by a dermatologist), and elevated liver enzymes (aspartate aminotransferase, AST activity > 33U/L; alanine aminotransferase, ALT activity > 33 U/L for males and > 25 U/L for females). On every follow-up visit, clinical assessments were combined with a physical examination by the dermatologist to identify skin rash (allergic reaction caused by NVP), fever, anaemia, Steven Johnson Syndrome, or toxic epidermal and necrolysis caused by NVP. AST and ALT levels were measured in 500 ul serum from patient using the RXmonza Semi-Automated Chemistry Analyzer (Randox Laboratories Ltd, United Kingdom). Following the manufacturer's (Randox Laboratories Ltd., United Kingdom) protocol, the reagents were reconstituted. 50 ul of the serum was added to 500ul of working reagent and vortexed briefly. The manufacturer's protocol was followed to calculate the AST and ALT serum levels after three absorbance values were taken at 1-minute intervals. Patients were characterised for two key functional single nucleotide polymorphisms (SNPs): *CYP2B6c.983T > C* (rs28399499) and *SULT1A1c.638G >A* (rs9282861).

SNP Genotyping

Genomic DNA was extracted from each whole blood sample using a Quick-gDNA Blood Miniprep (Inqaba Biotechnical, Pretoria, South Africa) according to the manufacturer's instructions. The eluted genomic DNA (stored at -20 ºC) was used to genotype the specific alleles of interest. Genotyping of the specific alleles for *CYP2B6c*.983T > C and *SULT1A1c*.638G > A was performed using PCR-RFLP as previously described [23,24], with some modifications. For *CYP2B6c*.983T > C,

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annealing temperature was 58 ºC for 30 secs and a final PCR reaction volume of 20 ul was used. CYP2B6c.983T > C primers used were 5'AGGAATCCACCCACCTCA AC3' and 5'GATAAGGCAGGTGAAGCAATCA3' as forward and reverse, respectively.

PCR for CYP2B6c.983T > C was in a 20 µl total reaction volume. The reaction mixture was made up of One Taq Quick-Load 2X Master Mix Standard Buffer (New England Biolabs), 10 µM forward (5'AGGAATCCACCCACCTC AAC3') and reverse (5'GATAAGGCAGGTGAAGCAAT CA3') primers, nuclease-free water, genomic DNA. Two per cent (2 % w/v) agarose gel stained with ethidium bromide was used to separate DNA fragments after PCR. Five microliters (5 µl) aliquot of the PCR product already containing a loading dye were loaded into each well in the agarose gel with 1X Tris cetic acid Ethylene diamine tetra-acetic acid (TAE) buffer. The setup was electrophoresed at 110 V for 40 minutes, visualised by an ultraviolet transilluminator and photographed. Aliquots of the PCR product were digested with the appropriate restriction enzyme (BsAmI) (New England Biolabs) in a 15 µl total mixture. The reaction mixture in a sterile Eppendorf tube was incubated in a water bath for 2 hours at 55 ºC. Two per cent (2% w/v) agarose gel (stained with ethidium bromide) electrophoresis was run at 110 V for the identification of the restriction fragments. A 100 bp DNA ladder was run on each gel to allow for fragment size determination.

For *SULT1A1c*.638G > A, the primers used were 5'GTTGGCTCTGCAGGGTTTCTAGGA3' and 5'CCCA AACCCCCTGCTGGCCAGCACCC3' as forward and reverse primers respectively. The PCR reaction was performed in a 24 µl total reaction volume. The reaction mixture was made up of One Taq Quick-Load 2X Master Mix Standard Buffer (New England Biolabs), 10 µM primers, nuclease-free water and genomic DNA. Two per cent (2% w/v) agarose gel stained with ethidium bromide was used to separate DNA fragments after PCR. Five microliters (5 µl) aliquot of the PCR product already containing a loading dye was loaded into each well in the agarose gel with 1X TAE buffer. The setup was electrophoresed at 110 V for 40 minutes using a mini-gel system, visualised by ultraviolet transillumination and photographed. Aliquots of the PCR product were digested with the appropriate restriction enzyme (HaeII) (New England Biolabs) in a 20 µl total mixture. The reaction mixture in a sterile Eppendorf tube was incubated in a water bath for 3 hours at 37 ºC. Three per cent (3% w/v) agarose gel (stained with ethidium bromide) electrophoresis was run at 110 V for the identification of the restriction fragments. A 100 bp DNA ladder was run on each gel to allow for fragment size determination.

Statistical analysis

The data obtained were analysed using Stata® version 14.2. CYP2B6c.983T > C and SULT1A1c.638G > A alleles and genotypes were summarised as frequencies and proportions. Logistic regression was used to explore the association between the observed genotype and NVP hypersensitivity at a 95% confidence interval. A p-value less than 0.05 was considered statistically significant.

RESULTS

Table 1 summarises the baseline clinical and demographic characteristics of the study participants. The majority (77.1%) of the study participants were females. The mean age of the participants was 38 ± 9.47 years with most of the participants between the ages of 31 - 49 years. A proportion of 17.1% developed NVPhypersensitivity (cases) while 82.9% were NVPtolerant (controls).

Figure 1 and Figure 2 represent PCR-RFLP Gel electrophoregram for CYP2B6c.983T > C and SULT1A1c.638G > A respectfully. In Figure 1, the amplicon of size 759 bp was digested with endonuclease BsmAI resulting in fragments size 759 bp for extensive metabolisers, 637 bp for intermediate metabolisers and 759 bp and 637 bp for poor metabolisers. In Figure 2, the amplicon size of 333 bp was digested with endonuclease

Table 1. Patient Demographics

Data Characteristics at baseline	Value
Age, mean ± SD, years	38.0 ± 9.5
Gender, number (%)	
Male	16 (22.9)
Female	54 (77.1)
Body Mass Index, mean ± SD, Kg/m^2	20.0 ± 2.8
CD4 cell count, mean ± SD, cells/mm^3	122.7 ± 112.7
Alanine aminotransferase, mean ± SD, U/L	29.4 ± 21.6
Aspartate aminotransferase, mean ± SD, U/L	44.8 ± 34.7

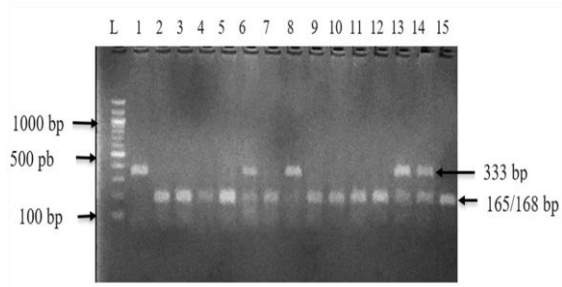

Figure 2: *SULT1A1c.638G>A* PCR-RFLP Gel electrophoregram.

A 3% agarose gel electropherogram showing RFLP results for *SULT1A1 638G>A* using *HaeII* restriction enzyme. L= 100 bp molecular ladder, Lane 1 and 8 = mut/mut (A/A), Lane = 2, 3, 4, 5, 7, 9-12 and 15 = wt/wt (G/G). Lane = 6, 13 and 14 = wt/mt = (G/A).

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HaeII resulting in fragment. In Figure 2, the amplicon size of 333 bp was digested with endonuclease HaeII resulting in fragment sizes 168 bp and 165 bp as extensive metabolisers, 333 bp, 168 bp and 165 bp as intermediate metabolisers and 333bp as poor metabolisers. Genotype frequencies summarised in Table 2 show that the T/T (extensive metabolisers) and T/C (intermediate metabolisers) of *CYP2B6**18c.983T > C variant alleles were present in 0.943 and 0.057 of the study participants respectively. No C/C (Poor metabolisers) were identified among the study participants. For the *SULT1A1c*.638G > A variant, the G/G (extensive metabolisers), G/A (intermediate metabolisers), and A/A (poor metabolisers) were present in frequencies of 0.614, 0.343, and 0.043, respectively. *CYP2B6c*.983T > C and *SULT1A1c*.638G > A were not associated with the development of NVP hypersensitivity.

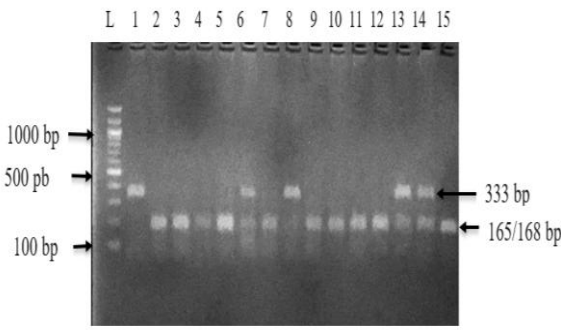

Figure 2. SULT1A1c.638G > A PCR-RFLP Gel electrophoregram.

DISCUSSION

The use of nevirapine in many developing countries has been associated with induced hypersensitivity reactions, and this is a contributory factor for patients defaulting to therapy. Genetic variants of *CYP2B6* and SULT1A1 may affect NVP metabolism and predispose patients to developing NVP hypersensitivity [5,13]. CYP2B6c.983T > C has been associated with the developing of NVP-hypersensitivity in some African populations *[13,16]*. *SULT1A1* sulfonation of 12-OH-NVP to 12-SUL-NVP, where 12-SUL-NVP forms adducts with proteins in the liver and skin, could also be a pathway for NVP-hypersensitivity [25]. We genotyped CYP2B6 and *SULT1A1* variants to determine if *CYP2B6c*.983T > C and *SULT1A1c*.638G > A variant could be associated with the development of NVP hypersensitivity in the Ghanaian population.

For *CYP2B6c*.983T > C, the extensive metabolisers (*CYP2B6* 983T/T) were more than the intermediate metabolisers (*CYP2B6* 983T/C) with no poor metaboliser genotype (*CYP2B6* 983C/C) recorded. The absence of poor metabolisers (*CYP2B6* 983C/C) in our study was not unusual, as similar findings have been reported in other African populations [12,26]. On the contrary, Maseng Tawe [27] recorded a frequency of 0.092 for poor metabolisers in Botswana, while Kwara and Lartey [28] reported a very low genotypic frequency of 0.001 for poor metabolisers in the Ghanaian population. This may imply that although the variant allele is prevalent in Africans, the poor metabolisers may be rare in the Ghanaian population. In the absence of therapeutic monitoring, reduction in NVP among *CYP2B6**18 poor metabolisers is recommended in order to minimise NVP-induced ADR [29]. The

Table 2. Genotype and Allele frequencies of *CYP2B6c*.983T > C and *SULT1A1c*.638G > A in HIV-1 patients

			Cases (n = 12)	Control (n = 58)	All (n = 70)		
SNP Characteristics	Genotype	Phenotype	Frequency (%)	Frequency (%)	Frequency (%)	OR [95% CI]	p-value
*CYP2B6*c.983T > C (rs28399499)	T/T	Extensive Metabolizer	11 (91.7)	55 (94.8)	66 (94.3)	1.00	
	T/C	Intermediate Metabolizer	1 (8.3)	3 (5.2)	4 (5.7)	1.667 (0.029-22.915)	0.668
	C	Minor allele	1 (4.2)	3 (2.6)	4 (2.9)	-	-
*SULT1A1*c.638G > A (rs9282861)	G/G	Extensive Metabolizer	8 (67.0)	36 (62.0)	43 (61.4)	1.00	
	G/A	Intermediate Metabolizer	4 (33.3)	19 (32.8)	24 (34.3)	0.947 (0.185-4.127)	0.936
	A/A	Poor Metabolizer	0 (0.0)	3 (5.2)	3 (4.3)	NE	0.418
	A	Minor allele	4 (16.7)	25 (21.6)	30 (21.4)	-	-

Cases; Nevirapine-Hypersensitivity, Control; Nevirapine-tolerant, CI; confidence interval, p-value < 0.05 is considered significant.

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intermediate metabolisers are associated with higher plasma NVP levels or decreased nevirapine clearance as well as a higher risk of developing NVP-hypersensitivity compared to the extensive metabolisers [12,16,30,31]. The *CYP2B6**18c.983T > C variant frequency (0.029) observed in our study is similar to those observed in African-Americans (0.029) and the Ghanaian populations (0.031) [19] but a slightly lower frequency of 1.6% observed in the Guinea population [18]. However, this variant was absent in Papua New Guinea, Caucasian-Americans and Asian-Americans [18]. This is an indication that there is a genetic variation between Africans and Caucasians for CYP2B6 metabolising enzymes, hence variations in response to drugs metabolised by CYP2B6.

We report that *CYP2B6c*.983T > C variant was not statistically associated with developing NVP-hypersensitivity, contrary to what has been observed in other African populations [13,16]. *CYP2B6* functional polymorphism 983T > C can be linked with 785A > G as a *CYP2B6**16 allele, resulting in a haplotype effect [18]. *CYP2B6**16 is known to be common among Africans [32], hence a significant association of the *CYP2B6**18 to nevirapine hypersensitivity could be a haplotype effect of *CYP2B6**16. In a study, *CYP2B6c*.516G > T and *CYP2B6c*.983T > C together were associated with up to five-fold higher mean plasma efavirenz (EFV) plasma concentrations, suggesting an additive effect of these polymorphisms [32]. Nuclear receptor genes NR112 and NR113, which regulate the transcription of *CYP2B6,* may also be possible genetic risk factors of NVP-hypersensitivity, although we did not consider these regulatory genes in our study.

SULT1A1 638 G > A has been studied among patients on HIV therapy and shown to significantly impact EFV plasma concentration [33,34]. The observed *SULT1A1c*.638G > A frequency of 0.214 was similar to those reported in African Americans [35]. *SULT1A1c*.638G > A poor metabolisers are expected to lead to a decreased reactive metabolite (12-SUL-NVP) plasma concentration, resulting in a low risk of developing NVP-hypersensitivity [20]. We report that *SULT1A1c*.638G > A variant was not statistically associated with developing NVP-hypersensitivity. Likewise, in a study by Sharma Novalen [25], the use of dehydroepiandrosterone, a *SULT1A1* inhibitor, did not prevent NVP-hypersensitivity, although there was a decreased plasma concentration of 12-OH-NVP. Inactivation of 12-OH-NVP could be due to other phase II metabolising enzymes. The 12-OH-NVP which is a substrate for SULT, can also be metabolised to 4-carboxy-NVP, escaping the SULT metabolising pathway (21). The risk of developing NVP-hypersensitivity is high in patients with combined null genotypes of glutathione S-transferase (GSTT1 and GSTM1) [36]. *CYP2B6**16 haplotype and other phase II metabolising enzymes may be contributory factors to developing NVP-hypersensitivity.

Conclusion

This study has reported for the first time, the prevalence of *SULT1A1c*.638G > A among the Ghanaian population. *CYP2B6c*.983T > C and *SULT1A1c*.638G > A variants were not associated with nevirapine-induced hypersensitivity among the patients. The poor metaboliser genotype (*CYP2B6* 983C/C) was not detected and may be very rare in the Ghanaian population.

DECLARATIONS

Ethical consideration

The study was approved by the College of Health Sciences Ethical and Protocol Review Committee of the University of Ghana [Reference number: CHS-Et/M.8-P 4.6/2016-2017]. All participants provided signed informed consent forms for the study. The HIV clinic (fevers unit) of the Department of Medicine of the Korle-Bu Teaching Hospital gave permission for the use of the data and patient samples.

Consent to publish

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None

Competing Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Author contributions

IEP and JIA participated in the laboratory analysis and manuscript writing. WK and ETN designed the research concept. ETN assisted with data analysis and interpretation. ETA assisted with the manuscript writing and helped transform the manuscript into an intellectual context.

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Availability of data

Data is available upon request to the corresponding author.

REFERENCES

1. Mikkelsen E, Hontelez JA, Jansen MP, Bärnighausen T, Hauck K, Johansson KA, et al. (2017) Evidence for scaling up HIV treatment in sub-Saharan Africa: A call for incorporating health system constraints. PLoS Med 14:1–5

2. Sherfa A, Haile D, Yihune M, Sako S. (2021) Incidence and predictors of adverse drug reaction (ADR) among adult HIV-positive patients on anti-retroviral treatment in Arba Minch town public health facilities, southern Ethiopia: A retrospective cohort study. PLoS One 16:e0251763

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3. García-Blanco D, Gravier-Hernández R, Rabeiro-Martínez CL, Valle LGd, Pérez-Ávila J. (2019) Pharmacogenetic markers: A path toward individualised HIV therapy. MEDICC Rev 21:59–68

4. Sevrioukova IF, Poulos TL. (2017) Structural basis for regiospecific midazolam oxidation by human cytochrome P450 3A4. Proc Natl Acad Sci USA 114:486–491

5. Kurogi K, Cao Y, Segawa K, Sakakibara Y, Suiko M, Uetrecht J, et al. (2022) Sulfation of 12-hydroxy-nevirapine by human SULTs and the effects of genetic polymorphisms of SULT1A1 and SULT2A1. Biochem Pharmacol 204:115243

6. Telenti A. (2004) Polymorphisms, resistance and drug response: beyond subtype-B HIV-1. Antivir Ther 9:1

7. Barco EA, Nóvoa SR. (2013) The pharmacogenetics of HIV treatment: A practical clinical approach. J Pharmacogenom Pharmacoproteomics 4:10

8. Pavlos R, McKinnon EJ, Ostrov DA, Peters B, Buus S, Koelle D, et al. (2017) Shared peptide binding of HLA Class I and II alleles associate with cutaneous nevirapine hypersensitivity and identify novel risk alleles. Sci Rep 7:1–12

9. Sarfo FS, Sarfo MA, Norman B, Phillips R, Chadwick D. (2014) Incidence and determinants of nevirapine and efavirenz-related skin rashes in West Africans: nevirapine's epitaph? PLoS One 9:1–7

10. Kudzi W, Aboagye E, Dzudzor B, Nartey E, Achel D. (2017) Risk factors of nevirapine hypersensitivity reaction among human immunodeficiency virus-1 infected treatment naïve patients at Korle-Bu Teaching Hospital. J AIDS Clin Res 8

11. Estes KE, Busse KH, Penzak SR. (2007) Pharmacogenetic considerations in the management of HIV infection. J Pharm Pract 20:234–245

12. Dickinson L, Chaponda L, Carr DF, van Oosterhout JJ, Kumwenda J, Lalloo DG, et al. (2014) Population pharmacokinetic and pharmacogenetic analysis of nevirapine in hypersensitive and tolerant HIV-infected patients from Malawi. Antimicrob Agents Chemother 58:706–712

13. Carr DF, Chaponda M, Cornejo Castro EM, Jorgensen AL, Khoo S, Van Oosterhout JJ, et al. (2014) CYP2B6 c. 983T> C polymorphism is associated with nevirapine hypersensitivity in Malawian and Ugandan HIV populations. J Antimicrob Chemother 69:3329–3334

14. Kranendonk M, Alves MN, Antunes P, Rueff J. (2014) Human sulfotransferase 1A1-dependent mutagenicity of 12-hydroxy-nevirapine: the missing link? Chem Res Toxicol 27:1967–1971

15. Paganotti GM, Russo G, Sobze MS, Mayaka GB, Muthoga CW, Tawe L, et al. (2015) CYP2B6 poor metaboliser alleles involved in efavirenz and nevirapine metabolism: CYP2B6* 9 and CYP2B6* 18 distribution in HIV-exposed subjects from Dschang, Western Cameroon. Infect Genet Evol 35:122–126

16. Ciccacci C, Di Fusco D, Marazzi MC, Zimba I, Erba F, Novelli G, et al. (2013) Association between CYP2B6 polymorphisms and nevirapine-induced SJS/TEN: a pharmacogenetics study. Eur J Clin Pharmacol 69:1909–1916

17. Yuan J, Guo S, Hall D, Cammett AM, Jayadev S, Distel M, et al. (2011) Toxicogenomics of nevirapine-associated cutaneous and hepatic adverse events among populations of African, Asian, and European descent. AIDS 25:1271

18. Mehlotra RK, Bockarie MJ, Zimmerman PA. (2007) CYP2B6 983T> C polymorphism is prevalent in West Africa but absent in Papua New Guinea: implications for HIV/AIDS treatment. Br J Clin Pharmacol 64:391–395

19. Klein K, Lang T, Saussele T, Barbosa-Sicard E, Schunck W-H, Eichelbaum M, et al. (2005) Genetic variability of CYP2B6 in populations of African and Asian origin: allele frequencies, novel functional variants, and possible implications for anti-HIV therapy with efavirenz. Pharmacogenet Genomics 15:861–873

20. Heck CJ, Seneviratne HK, Bumpus NN. (2020) Twelfth-position deuteration of nevirapine reduces 12-hydroxy-nevirapine formation and nevirapine-induced hepatocyte death. J Med Chem 63:6561–6574

21. Caixas U, Antunes AM, Marinho AT, Godinho AL, Grilo NM, Marques MM, et al (2012) Evidence for nevirapine bioactivation in man: searching for the first step in the mechanism of nevirapine toxicity. Toxicology. 301:33-9.

22. Kurogi K, Rasool MI, Alherz FA, El Daibani AA, Bairam AF, Abunnaja M, et al. (2021) SULT genetic polymorphisms: physiological, pharmacological and clinical implications. Expert Opin Drug Metab Toxicol 17:237–249

23. Rohrich CR, Drogemoller BI, Ikediobi O, van der Merwe L, Grobbelaar N, Wright GE, et al. (2016) CYP2B66 and CYP2B618 predict long-term efavirenz exposure measured in hair samples in HIV-positive South African women. AIDS Res Hum Retroviruses 32:529–538

24. Wang Y, Spitz MR, Tsou AM, Zhang K, Makan N, Wu X (2002) Sulfotransferase (SULT) 1A1 polymorphism as a predisposition factor for lung cancer: a case-control analysis. Lung Cancer 35:137–142

25. Sharma AM, Novalen M, Tanino T, Uetrecht JP (2013) 12-OH-nevirapine sulfate, formed in the skin, is responsible for nevirapine-induced skin rash. Chem Res Toxicol 26:817–827

26. Isaac A, Wetkos D, Oche A, Godwin I, Phyllis K, John A (2020) Prevalence of cytochrome P450 2B6 single nucleotide polymorphism in an HIV-positive cohort in Jos, Nigeria: implication for HIV therapy. Niger J Clin Pract 23:1736–1741

27. Maseng MJ, Tawe L, Thami PK, Seatla KK, Moyo S, Martinelli A, et al. (2021) Association of CYP2B6 genetic variation with efavirenz and nevirapine drug resistance in HIV-1 patients from Botswana. Pharmacogenomics Pers Med 14:335–349

28. Kwara A, Lartey M, Sagoe KW, Kenu E, Court MH (2009) CYP2B6, CYP2A6 and UGT2B7 genetic polymorphisms are predictors of efavirenz mid-dose concentration in HIV-infected patients. AIDS 23:2101–2109

29. Schipani A, Wyen C, Mahungu T, Hendra H, Egan D, Siccardi M, et al. (2011) Integration of population pharmacokinetics and pharmacogenetics: an aid to optimal nevirapine dose selection in HIV-infected individuals. J Antimicrob Chemother 66:1332–1339

30. Oluka MN, Okalebo FA, Guantai AN, McClelland RS, Graham SM (2015) Cytochrome P450 2B6 genetic variants are associated with plasma nevirapine levels and clinical response in HIV-1 infected Kenyan women: a prospective cohort study. AIDS Res Ther 12:1–9

31. Mahungu T, Smith C, Turner F, Egan D, Youle M, Johnson M, et al. (2009) Cytochrome P450 2B6 516G→T is associated with plasma concentrations of nevirapine at both 200 mg twice daily and 400 mg once daily in an ethnically diverse population. HIV Med 10:310–317

32. Wang J, Sönnerborg A, Rane A, Josephson F, Lundgren S, Ståhle L, et al. (2006) Identification of a novel specific CYP2B6 allele in Africans causing impaired metabolism of the HIV drug efavirenz. Pharmacogenet Genomics 16:191–198

33. Chamnanphon M, Sukprasong R, Gaedigk A, Manosuthi W, Chariyavilaskul P, Wittayalertpanya S, et al. (2021) Influence of SULT1A1*2 polymorphism on plasma efavirenz concentration in Thai HIV-1 patients. Pharmacogenomics Pers Med 14:915–924

34. Haas DW, Kwara A, Richardson DM, Baker P, Papageorgiou I, Acosta EP, et al. (2014) Secondary metabolism pathway polymorphisms and plasma efavirenz concentrations in HIV-infected adults with CYP2B6 slow metaboliser genotypes. J Antimicrob Chemother 69:2175–2182

35. Carlini EJ, Raftogianis RB, Wood TC, Jin F, Zheng W, Rebbeck TR, et al. (2001) Sulfation pharmacogenetics: SULT1A1 and SULT1A2 allele frequencies in Caucasian, Chinese and African-American subjects. Pharmacogenet Genomics 11:57–68

36. Singh H, Lata S, Angadi M, Bapat S, Pawar J, Nema V, et al. (2017) Impact of GSTM1, GSTT1 and GSTP1 gene polymorphism and risk of ARV-associated hepatotoxicity in HIV-infected individuals and its modulation. Pharmacogenomics J 17:53–59