

Adverse Drug Reactions Associated with CYP 2B6 Polymorphisms in HIV/AIDS-Treated Patients in Yaoundé, Cameroon

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Purpose: The metabolism of antiretroviral drugs is subject to individual variations of the CYP 2B6 gene. The objective of this study was to evaluate the prevalence of CYP 2B6 516 G>T and 983 T>C polymorphisms and investigate their association with the development of adverse drug reactions (ADRs) in people living with HIV/AIDS in Cameroon.

Patients and methods: A total number of 122 patients, attending the Yaoundé Central Hospital HIV Day Clinic, consented to take part in this study. Blood specimens were collected and DNA was extracted using the Chelex method. Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) was performed for the detection of CYP 2B6 Single-Nucleotide Polymorphisms (SNPs). Genotype frequencies were compared between groups with or without ADRs. Logistic regression analysis was performed to assess association between genotype and adverse effects of antiretroviral therapy (ART).

Results: Three types of metabolizers were identified: extensive, intermediate and slow. For the 516G>T polymorphism, prevalences of 8.2% GG, 65.6% GT and 26.2% TT were obtained. For the 983T>C polymorphism, 89.3% TT, 4.1% CT and 6.6% CC prevalences were obtained. Those homozygous for the wild-type allele (516GG) were less likely to develop ADR with a statistically significant difference (OR=0.885, P=0.029). For the CYP2B6 T983C SNP, homozygous mutants (CC) may present a higher risk (threefold) of developing adverse reactions (OR=2.677, P=0.164).

Conclusion: These findings demonstrate that ADRs among HIV/AIDS patients under ART may be associated with the genetic variability of the metabolizing enzyme CYP 2B6. Genotyping for this gene may guide the better administration of Efavirenz and Nevirapine to Cameroonian patients.

Keywords: CYP 2B6 polymorphisms, association, adverse drug reactions, HIV/AIDS

Introduction

Acquired Immunodeficiency Syndrome (AIDS) is one of the greatest public health challenges, with a World Health Organization (WHO) estimate of 36.7 million people infected around the world, and sub-Saharan Africa as the most affected region – accounting for 64% of the global burden.¹ The disease is controlled by the administration of Antiretroviral Therapy (ART). The goals include the control of HIV replication; prevention of HIV transmission; reduction of HIV-related morbidity and mortality; and improving quality of life.² The first line recommended by WHO in resource-limited countries, including Cameroon, consists of two Nucleoside Reverse Transcriptase Inhibitors (NRTI) plus one Non-Nucleoside Reverse Transcriptase

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Inhibitors (NNTIs) where Efavirenz (EFV) or Nevirapine (NVP) are the two most commonly used.³

Drug treatment in HIV disease is characterized by a great variability in response, in terms of both efficacy and toxicity.⁴ Several factors may affect this variability and may include ethnicity, gender, age, body weight, drug–drug and drug–food interactions, binding to plasma proteins, hepatic impairment, disease status, pregnancy, and host genetic factors.⁵ The benefit of pharmacogenetic testing is to guide the choice of the initial drug regimen, thus increasing efficacy, and simultaneously avoiding ADRs.⁶ Genetic variations can impact the pathways of drug absorption, disposition, metabolism and excretion (ADME).⁷ A mutation in a gene coding for a drug-metabolizing enzyme can result in an enzyme with normal, low, or no activity.⁸ EFV and NVP are principally metabolized by cytochrome P450 2B6.^{9,10}

The gene that encodes for CYP2B6 is highly polymorphic.¹¹ Up to date, about 60 allelic variants have been reported.¹² Of these, CYP2B6 516G>T and 983T>C SNPs have been reported to be of clinical relevance.¹³ Several studies performed in Africa have reported that the CYP2B6 516G>T allele can occur in 20 to over 49% of the individuals.^{14–18} The second polymorphism is more frequent among African subjects with allele frequencies of 4–11%.^{13,19} These two polymorphisms have been associated with increased EFV and NVP plasma levels in several studies.^{20–28} A number of associations between these human genetic variants, high drug level and predisposition to ARV drug toxicity have been described in recent years.^{29–33} ADRs associated with NVP are cutaneous or dermatological events (toxidermia/hypersensitivity, skin rash, and pruritus). ADRs associated with EFV are central nervous events including insomnia, hallucinations, nightmares, headache, dizziness, and somnolence.

The objective of this work was to determine the frequency of CYP2B6 polymorphisms (516G>T and 983T>C) and the influence of their heterozygosity and homozygosity on the development of ADRs.

Materials and Methods

Study Setting, Design and Enrollment Procedure

The study was conducted in the Outpatients ART Centre of the Yaoundé Central Hospital (YCH), which is one of the largest in Cameroon. This unit was created in 1988 and follows about 10.000 HIV patients on ART treatment. The services provided include full consultation by devoted

physicians (5) and psychosocial counselors (70), a pharmacy for drug refills, and laboratory testings (CD4 count, viral load and others) for biological follow-up. It is open from 8:00 a.m. to 3:30 p.m., and is one of the two Teaching Hospitals in Yaoundé, the other being the University Teaching Hospital.

HIV-infected individuals already under ART, with or without ADRs, were selected retrospectively, based on information reported in their medical records by clinicians after consultation. A list of patients with their telephone numbers was thus constituted. ADRs were diagnosed, based on patient complaints and/or physical changes noticed by physicians during routine clinical exam. ADR is said to be associated with therapy when absent before treatment and present after treatment initiation. Controls were recruited from the same Health Center and were selected on the basis of the absence of ADR development during at least 2 years of treatment regimen containing NVP or EFV. Participants were prospectively recruited after contacting them through phone calls. A total of 35 patients who had developed ADRs associated with NVP or EFV and 87 controls were recruited.

- Inclusion criteria:
 - Under ART for at least 2 years
 - >18 years
 - Signed informed consent
 - Being followed up
- Exclusion criteria:
 - Withdrawal from the study.

Data Collection Procedure

Demographic, clinical and therapeutic data were obtained from clinical records of HIV/AIDS patients under ART who gave their informed consent. Such data included: sex, age, weight, CD4 cell counts, hemoglobin level, ART regimen, treatment initiation date, complaints after treatment initiation, ADR onset time, treatment modification and information on treatment observance or adherence.

Sample Collection and DNA Extraction

Five (5) mL of venous blood were collected and used to prepare dried blood spots on filter paper that were stored until genomic analysis. DNA was extracted using the Chelex method as previously described.³⁴ The final supernatant (DNA) was transferred into a fresh tube and stored in TE buffer at –20°C for further pharmacogenetic analyses.

Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP)

Two alleles – CYP2B6 516G>T (rs3745274) and CYP 2B6 983T>C (rs28399499) – were investigated using PCR-RFLP. The primer sequences used to amplify the genes were CYP 516 F: 5'-GGT CTG CCC ATC TAT AAA C-3' and CYP 516 R: 5'-CTG ATT CTT CAC ATG TCT GCG-3', CYP 983 F: 5'-AGG AAT CCA CCC ACC TCA AC-3' and CYP 983 R: 5'-GAT AAG GCA GGT GAA GCA ATC A-3', respectively. The amplification was done in a T3 thermal cycler (Biometra, UK). Each PCR cycle was performed in a total volume of 25 μ L containing: nuclease-free water, 10 \times ThermoPol buffer, 10 mM dNTPs (200 μ M of each deoxyribonucleotide), 20 pmol of primer, 5 U/ μ L of Taq polymerase and 3 ng of gDNA. For 516 G>T, after initial denaturation at 95°C for 10 min, 35 cycles of amplification were carried out with denaturation at 94°C for 30 s, annealing at 58°C for 30 s and extension at 72°C for 60 s, followed by a final extension at 72°C for 10 min and then conservation at 4–8°C for 48 h. For 983T>C, the conditions were different at the level of annealing (59°C for 25 s) and the total number of cycles 45. To confirm the presence of CYP 2B6 gene, the expected amplicon sizes of the PCR products (526bp and 759bp, respectively) were verified on 2% agarose gel electrophoresis. The RFLP reaction conditions for digestion with BSrI (for 516 G>T) and BSmaI (for 983 T>C) (New England Biolabs, USA) were set at 65°C and at 55°C, respectively, both for 16 h each. The products of the digestion reaction were separated on a 2% agarose gel stained with ethidium bromide. Polymorphisms were determined according to specific fragment patterns as follows:

- (516 G/G): 268 bp, 236 bp, 22 bp
- (516 G/T): 504 bp, 268 bp, 236 bp, 22 bp
- (516 T/T): 504 bp, 22 bp
- (983 T/T): 759 bp
- (983 C/T): 759 bp, 637 bp, 122 bp
- (983 C/C): 637 bp, 122 bp

Compliance with Ethical Standards

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. An ethical clearance was obtained

from the Comité National d'Ethique de la Recherche pour la Santé Humaine (N° 2014/12/670/CE/CNERSH/SP).

Informed Consent

A written informed consent was obtained from each participant included in the study.

Data Analyses

All data were entered into Excel files and analyzed using the Statistical Package for Social Sciences (SPSS) version 16.0 (SPSS Inc., USA) statistical software. Frequencies of the CYP2B6 516G>T and 983T>C genotypes in the study population were obtained by descriptive statistics. The Chi-square test was used to assess the association between ADRs and baseline characteristics. The association between the genotype/phenotype of the CYP2B6 516G>T and 983T>C and adverse effects of ART (NVP and EFV) in the study population was evaluated by binary logistic regression analysis. The odds ratios (ORs) at 95% confidence intervals (CIs) were also calculated and the cut-off for statistical significance was set at a p value of <0.05.

Results

Study Population Characteristics

Of the 122 participants recruited, 74 (61%) were females while 48 (39%) were males. The mean age was 37.5 years with an average weight of 61.52 kg. Average hemoglobin was 10.82 g/dl and the mean CD4 cell count Pre-ART was 185.52 cells/mm³ (Table 1). Table 2 depicts the distribution of ADRs according to sex, age, weight, CD4 and hemoglobin. There were no statistically significant differences among the groups.

Adverse Reactions Reported Following ART Administration

For this study, we enrolled 87 patients with no ADRs (controls) and 35 with reported ADRs (cases). Among

Table 1 Baseline Characteristics of the Study Population

Variables	Minimum	Maximum	Mean \pm Std Deviation
Age (years)	19	64	37.50 \pm 10.475
Weight (kg)	40	99	61.52 \pm 10.41
Hemoglobin (g/dl)	4	19	10.82 \pm 2.515
CD4 (cells/mm ³)	7	426	185.52 \pm 105.23

Table 2 Distribution and Association of Adverse Drug Reactions with Baseline Characteristics

Variable	Adverse Drug Reactions		Total	p value
	Yes	No		
Sex				
Female	17	57	74	0.083
Male	18	30	48	
Total	35	87	122	
Age (years)				
≤45	26	69	95	0.545
>45	9	18	27	
Total	35	87	122	
Weight (kg)				
≤50	6	15	21	0.989
>50	29	72	101	
Total	35	87	122	
CD4 (cells/mm³)				
≤200	17	50	67	0.371
>200	18	37	55	
Total	35	87	122	
Hemoglobin (g/dl)				
≤10	13	34	47	0.842
>10	22	53	75	
Total	35	87	122	

the 35 cases, 19 had developed cutaneous adverse events (toxicodermia/hypersensitivity) and the rest (16) reported central nervous adverse events including insomnia, hallucinations, nightmares, headache, dizziness, and somnolence. The mean onset time (duration of patients on ART before developing reported ADR) was 2.69 (1–6) weeks. Additionally, in all of them, the treatment was modified due to these ADRs. Eight participants self-reported poor respect of treatment prescription.

Genotype and Allele Frequencies of CYP2B6 516G>T SNP Among Study Participants

The number of individuals presenting the CYP2B6 516GG wild-type genotype (extensive metabolizers) was 10 (8.2%). Seventy-nine (65.576%) participants had the heterozygous GT genotype (intermediate metabolizers) while 33 (26.23%) expressed the homozygous TT genotype considered as poor metabolizers (Figure 1). Allele frequencies for the CYP2B6 516G>T SNP were 40.96% for the G allele and 59.04% for the C allele.

Genotype and Allele Frequencies of CYP2B6 983 T>C SNP Among Study Participants

The number of individuals presenting the CYP2B6 983TT wild-type genotype (extensive metabolizers) was 109 (89.3%). Five (4.1%) had the heterozygous CT genotype (intermediate metabolizers) while eight (6.6%) expressed the homozygous CC genotype considered as poor metabolizers (Figure 2). Allele frequencies for the CYP2B6 983T>C SNP were 94.4% for T allele and 5.6% for C allele.

Association Between CYP2B6 516G>T SNP and CYP2B6 983T>C SNP Genotype/Phenotype of Participants and ADR

Association analysis of the CYP2B6 516G>T SNP showed that individuals homozygous for the wild-type allele were likely to have some degree of protection against ADRs with a statistically significant difference as compared to heterozygous and the mutants (OR=0.885, P=0.029). Additionally, the results showed that Individuals with heterozygous and homozygous mutants were at risk to develop ADRs (OR=1.208 and OR=1.34, respectively) although with no significant difference between them (P=0.416 and P=0.317, respectively). For the CYP2B6 T983C SNP, homozygote genotypes (CC) had a three times higher risk of developing adverse reactions (OR=2.677), but the difference with heterozygous and wild types was not statistically significant (P=0.164) (Table 3).

Haplotypes were constructed with the two variants explored in this study. The most frequent one was the 516GT/983TT and the 516GG/983CC was totally absent in the study population (Table 4).

Discussion

Data obtained on the distribution of genetic variations in populations are important in helping to understand inter-individual differences in response to treatment or drug. The association of the CYP 2B6 516 G>T and 983 T>C polymorphisms with Efavirenz and Nevirapine metabolism is well established. The frequencies of these SNPs were determined and their association with the development of adverse drug reactions to ART (NVP and EFV) investigated.

For the CYP 2B6 516 G>T polymorphism, individuals having the GG, GT and TT genotypes in our study population

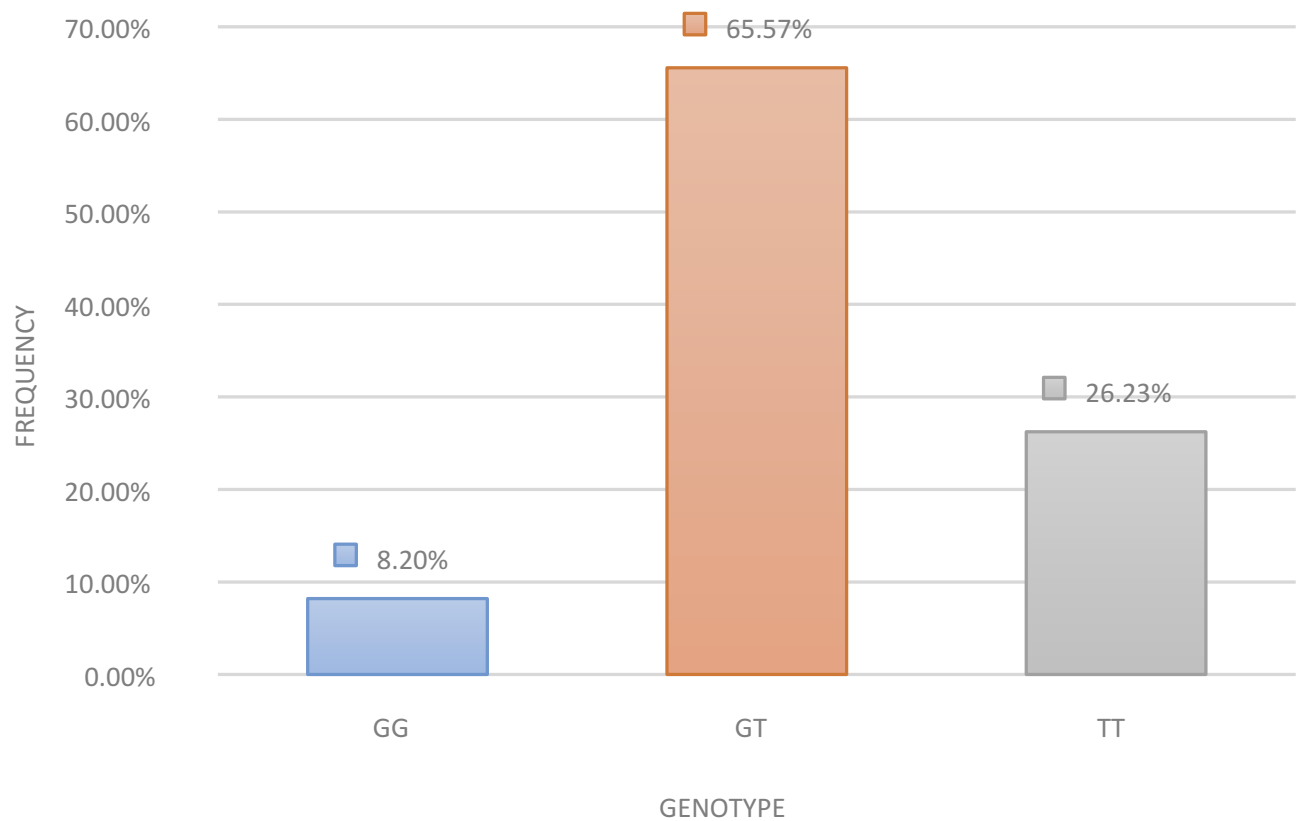


Figure 1 Genotype frequencies for the CYP2B6 516G>T SNP in the study population.

Abbreviations: GG, Extensive Metabolizer; GT, Intermediate Metabolizer; TT, Slow metabolizer.

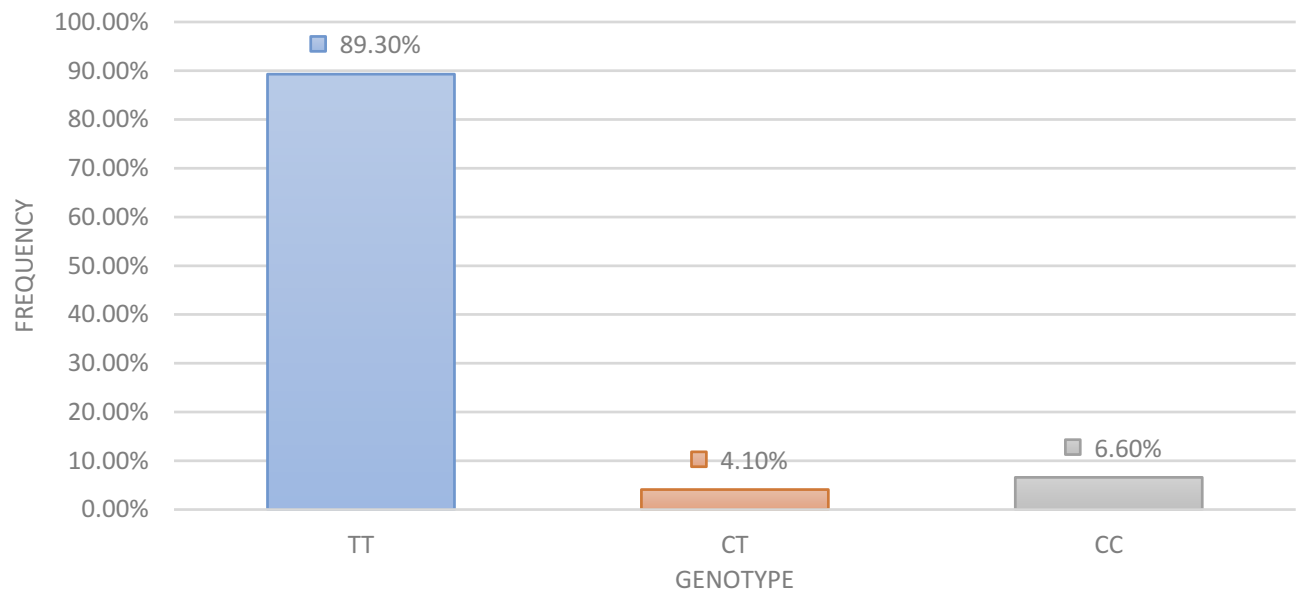


Figure 2 Genotype frequencies for the CYP2B6 983T>C SNP in the study population.

Abbreviations: TT, Extensive Metabolizer; CT, Intermediate Metabolizer; CC, Slow metabolizer.

represented 8.2%, 65.6%, and 26.2%, respectively. The prevalence of TT in this study was lower than in West Africa (54%), Papua New Guinea (33%),³⁵ Spain (40%)³⁶

and Japan (32.6%).³⁷ In Caucasians, Cambodians, and Burundese, considerably lower values of 5.9%, 9.2%, and 13%, respectively, were reported.^{21,38,39} Some studies in

Table 3 Association Between CYP2B6 516G>T SNP and CYP2B6 983T>C SNP Genotype/Phenotype of Participants with or Without ADR

SNP	Genotype	Adverse Drug Reactions		OR [95% CI]	p value
		Yes: n (%)	No: n (%)		
516 G>T	GG (EM)	0 (0)	10 (11.50)	0.885 [0.821–0.955]	0.029*
	GT (IM)	24 (68.57)	55 (63.22)	1.208 [0.523–2.791]	0.416
	TT(SM)	11 (31.43)	22 (25.28)	1.354 [0.572–3.206]	0.317
	Total	35 (100)	87 (100)		
T>C	TT (EM)	31 (88.57)	78 (89.65)	0.894 [0.256–3.119]	0.544
	TC (IM)	0 (0)	5 (5.75)	0.943 [0.895–0.993]	0.178
	CC (SM)	4 (11.43)	4 (4.60)	2.677 [0.631–11.369]	0.164
	Total	35 (100)	87 (100)		

Note: *Statistically significant p value.

Abbreviations: SNP, Single Nucleotide Polymorphism; OR, Odds Ratio; CI, Confidence Interval; EM, Extensive Metabolizer; IM, Intermediate Metabolizer; SM, Slow metabolizer; n, number; %, percentage.

Table 4 Different Haplotypes and Their Prevalence in the Study Population

Haplotypes	Number	Frequency (%)
516GG/983TT	9	7.38
516GG/983CT	1	0.82
516GG/983CC	0	0
516GT/983TT	71	58.20
516GT/983CT	3	2.46
516GT/983CC	6	4.92
516TT/983TT	29	23.77
516TT/983CT	1	0.82
516TT/983CC	2	1.64
Total	122	100%

India reported 20.56–28% which are closer to our results.^{40,41} Huang et al reported a very low prevalence of the TT genotype (1.8%) among the Taiwanese.⁴² Regarding the other SNP 983 T>C, we obtained 89.3% TT, 4.1% CT and 6.6% CC. These results were not in line with that of Blievernicht and collaborators who found that this mutation was completely absent among individuals of white European origin.³⁸

In our study, the minor allele frequencies for 516G>T and 983T>C were 0.41 (G) and 0.09 (C) respectively. These results were close to 0.34 and 0.07 obtained by Wyen et al on Germans,⁴³ but a study on Guineans reported a very low frequency (0.01) of this C allele.¹⁹ The prevalence of the T allele (516G>T), which was observed in this study, was higher (59%) than the (35%) reported elsewhere (in Cambodia).³⁹

It was observed that individuals homozygous for the wild-type allele (516 GG) were likely to be protected from ADR susceptibility with a statistically significant difference

compared to heterozygous and mutants (OR=0.885, P=0.029). This could be due to the fact that extensive metabolizers eliminate drugs from the system rapidly; thus, such people are not exposed to high drug levels in the plasma. Our results equally showed that heterozygous and homozygous mutants for the 516G>T are at risk of developing ADRs due to the presence of the non-functional alleles (OR=1.208 and/or=1.34, respectively). For CYP2B6 SNP, T983C, participants with the homozygous genotypes (CC) were more susceptible (threefold higher risk OR=2.677) to develop conditions like cutaneous adverse reactions, central nervous adverse events regrouping insomnia, hallucination, nightmare, headache, dizziness, and somnolence, compared to those with other genotypes, although with no significance (P=0.164). This could be due to the fact that slow metabolizers eliminate drugs from the system slowly, thus leading to drug persistence resulting in toxicity. Our results can be compared to other studies that reported an association between the presence of 516G>T or 983T>C, high plasma NVP or EFV concentrations and the susceptibility to related ADRs.^{16,29–31,33,44} The lack of a significant difference between the presence of the adverse events and the genotypes might have been due to the small sample size, particularly the number of cases, which is one of the limitations of this study. The other limitation was the retrospective aspect of the participants' selection. This study demonstrated that genetic variability in a metabolizing enzyme gene can also be correlated with susceptibility to ADR, a condition that should be considered. The fact that the association between ADR and both Efavirenz and Nevirapine was considered in this study is a strength because it was able to show that exposure to either of the drugs, your CYP 2B6 516G>T and 983 T>C

genotype can create susceptibility to develop adverse effects. This is the first study carried out on HIV-treated patients in Cameroon that has considered associating the presence of polymorphisms on the CYP 2B6 gene with the susceptibility to develop ADRs.

Conclusion

This study was able to show that CYP2B6 gene variants (T983C and G516T) are associated with susceptibility to adverse drug reactions induced by Efavirenz or Nevirapine in HIV/AIDS-infected Cameroonians. It was found that the 983CC genotype confers a significantly higher risk of developing ADR. These findings need to be validated by a larger population. The results of this study suggest that CYP2B6 genotyping may help in optimizing antiretroviral therapy in patients who initiate an EFV- or NVP-based combination as it will help in identifying patients who will be more likely to develop adverse drug reactions in Cameroon.

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Disclosure

The authors report no conflict of interest in this work.

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