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Cytochrome P450 2B6 6 distribution among patients living with HIV in Burkina Faso

Raoul KARFO[1,2*], Fabienne Marie SOUDRE[1], Alice KIBA[1], Arnaud KOURAOGO[4], Elie KABRE[1,3] and Jean SAKANDE[1,3]

[1] Training and Research Unit in Health Sciences, University Joseph Ki-Zerbo, Ouagadougou, Burkina Faso.
[2] Biology Laboratory Clinic, Camp General Aboubacar Sangoule Lamizana Medical Center, Ouagadougou, Burkina Faso.
[3]Laboratory of Biochemistry, University Hospital Yalgado Ouedraogo, Ouagadougou, Burkina Faso.
[4]Institute of Health sciences, University Nazi Boni, Bobo Dioulasso, Burkina Faso.
[*]Corresponding author; E-mail: rkarf006@yahoo.fr

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ABSTRACT

The function of cytochrome P450 (CYP) enzymes, one of the major catalysts in drug metabolism, is significantly influenced by genetic polymorphisms leading to substantial inter-individual variability in drug response and/ or adverse reactions activity. The aim of this study was to determine the frequency of the CYP2B6 516G>T allele in patients living with HIV receiving treatment at the Medical Center of Camp General Aboubacar Sangoule Lamizana for whom the treatment was changed after the initiation of treatment because of the appearance of side effects**.** 155 HIV-positive patients were enrolled. Genomic Deoxyribonucleic acid (DNA) extraction from blood was performed using the GenJET® Genomic DNA according to the manufacturer's instructions. Genotyping for the cytochrome P450 variant alleles was performed using predesigned primers. The amplification was carried out by Polymerase Chain Reaction (PCR), while the differentiation between the alleles was carried out after digestion with restriction enzymes by electrophoresis. The results obtained showed. Among these patients, 61 changed treatments during their follow-up. The majority of the 61 patients, 32 patients, received an initial treatment regimen based on the AZT (3'-Azido-3'-Deoxythymidine)/3TC (Lamivudine)/ NVP(Nevirapine) combination, followed by 18 patients for the TDF (tenofovir)/3TC (lamivudine)/ EFV(Efavirenz) regimens. Currently, the majority of patients, 48 patients, have benefited from a therapeutic regimen based on the TDF (tenofovir)/3TC (lamivudine) /DTG(Dolutegravir) combination, followed by 11 patients for the TDF (tenofovir)/3TC (lamivudine)/EFV(Efavirenz) regimens. The distribution of the major allele CYP2B6*T was 68%, and the minor CYP2B6*G allele was 32%. Heterozygote (GT genotype) and Homozygous mutants (TT genotype) and Heterozygote were 31% and 52,5%. Studies could be continued to set up cytochrome mutation detection kits to anticipate the onset of side effects and adapt treatments.

Keywords: CYP2B6 516 G>T, Correlation, clinical outcomes, HIV patients, Burkina Faso.

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INTRODUCTION

Cytochromes P450 (CYP450) constitute the main family of enzymes able to catalyze the oxidative biotransformation of most drugs and other lipophilic xenobiotics and are therefore particularly relevant for clinical pharmacology (Shaya et al., 2023; Esteves et al., 2021; Lorenzini et al., 2021; Munro et al., 2018; Guengerich, 2008**)**. The most common allele is CYP2B6*6, with two amino acid changes, Gln172His and Lys262Arg in combination with other identified changes mainly in the promoter (Mangó et al., 2022). In Burkina Faso, since 2008, the antiretrovirals (ARVs) available have been divided into six (6) drug classes: nucleotide/nucleotide reverse transcriptase inhibitors [NRTIs], nonnucleotide reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (IF), integrase inhibitors (II), and C-C chemokine receptor type 5 (CCR5) coreceptor inhibitors. Nonnucleoside reverse transcriptase inhibitors (NNRTIs) are potent and selective HIV reverse transcriptase inhibitors but are inactive against HIV-2 (Karatzas et al., 2019, Ezeugwunne et al., 2012). The molecules available are nevirapine (NVP), efavirenz (EFV), etravirine (ETV), and rilpivirine (RPV). The recommended therapeutic combination is the combination of 3 ARVs (triple therapy) from two different classes of ARVs: “2NRTIs+1NNRTIs” combination: indicated only in the event of HIV1 infection; "2NRTIs+1PI" combination: indicated in case of HIV 2 infection, HIV1 and 2 co-infection. Antiretroviral drugs are involved in the occurrence of adverse effects (Kouakou-Siransy et al., 2015). Cytochrome genotyping of CYP2B6 in people living with HIV on antiretroviral therapy, particularly those on efavirenz therapy is important. One study in China showed pharmacokinetic differences in HIV-infected patients with different genotypes of CYP2B6 516G/T who underwent antiviral therapy with efavirenz. The accumulation of efavirenz might occur over time, leading to neurotoxicity in subjects with TT and GT genotypes (To et al., 2009). The objective of our study was to determine the frequency of the CYP2B6 516G>T allele in patients living with HIV followed at the Medical Center of Camp General Aboubacar Sangoule Lamizana for whom the treatment was changed after the initiation of treatment because of the appearance of side effects.

MATERIALS AND METHODS

Study site

This was a study carried out over a period of five years in dermatology clinics, laboratories of the Medical Center of Camp Aboubacar Sangoulé Lamizana (CMCGASL), and in the Biochemistry Laboratory of the Faculty of Medicine of the Unit of Training and Research in Health Sciences at the Joseph KI ZERBO University.

Participants

The recruitment of patients takes place in a military structure. It is true that this structure follows civilian patients but especially military patients and their families. The strength of the armies is composed of an overwhelming majority of men. Consenting and enrollment were performed for 155 HIV patients receiving HIV care and treatment at the CMCGACL dermatology clinic. Patients were recruited in this study for CYP 2B6 genotyping if they were (i) aged above 18 years, (ii) consenting to the study, and (iii) the treatment was changed after the initiation of treatment because of the appearance of side effects.

Variables

Sociodemographic variables, HIV screening tests, cytochrome P450 genotyping.

Data collection

Sociodemographic information was collected on a survey sheet at the CMCGASL dermatology clinic.

HIV serology tests

HIV testing was performed according to a standard procedure recommended by national HIV testing guidelines using two rapid diagnostic tests (RDTs) in a sequential algorithm. The samples were tested using a first TDR (Determine Alere ® HIV1/2 Abbott

Alere Medical Co. Ltd, Matsudo, Japan). The samples that proved to be reactive with this first RDT were evaluated by a second immunochromatographic test (SD Bioline® HIV1/2 3.0 Standard Diagnostics, Giheung-gu, Yongin-si, Korea), which made it possible to specify the type of HIV (HIV1, HIV2, HIV1 and 2).

CYP2B6*6 genotyping

DNA preparation

Genomic DNA was extracted from EDTA-collected blood using the Gen JET Genomic DNA Purification kit (Thermo Scientific® Lithuania Kit) according to the manufacturer's instructions. The quality of DNA was measured using an ND-1000 UV spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA).

Restriction fragment length polymorphism (PCR-RFLP)

Single Nucleotide Polymorphism (SNP) was analyzed using polymerase chain reaction- restriction fragment length polymorphism technique for CYP2B6 516G>T (rs3745274). This technique takes place in several steps. First, 2 µL of 50 ng/µL DNA was added to each PCR tube separately and pipette tips were changed at each stage. The second step was the PCR MIX preparation in a total volume of 25 µL, as shown in Table 1. Mix properly by tapping or pulse mix. Add 23 µL of the PCR mix to each PCR tube, which already contains 2 µL of DNA. The PCR consisted of a denaturation step at 94°C for 3 minutes, 94°C for 30 seconds, annealing at 54°C for 30 seconds, extension at 72°C for 40 seconds, a final extension at 72°C for 10 minutes. Repeat steps denaturation at 94°C for 30 seconds annealing at 54°C for 30s, extension at 72°C for 40 seconds for 35 cycles. The primers for CYP2B6 516G>T (rs3745274) are CYP2B6-4F: 5'-GGTCTGCCCATCTATAAAC-3' and CYP2B6-4R: 5'-CTGATTCTTCACATGTCTGCG-3'. Finally, 5 µL of PCR product was placed on a 1.5% agarose gel stained with GRGreen (100 min, 100 V, 5 µL GeneRulerTM 100 bp DNA Ladder Plus). Expected PCR product: 526 bp DNA fragment. Quality of the PCR product was checked by visualization on a UV-doc system (Figure 1). If successful, 10 µL of each PCR product was added to a separate Eppendorf tube marked with the identity of each sample for digestion below. The digestion mix was prepared in a total volume of 30 µL as shows in Table 1. This technique is also used for the identification of bacteria (Azokpota et al., 2007). 20 µL of digestion mix was added to each tube with individual PCR products. Incubation was done over night at 60°C and enzymes inactivated for 5 min at 80°C. Agarose gel electrophoresis was then performed by loading 30 µL of the digestion product on a 2.5% agarose gel stained with GRGreen (60-180 mins, 80 V, 5 µl GeneRulerTM 100 bp DNA Ladder Plus) (Table 1). The results for this SNP were defined as homozygous wild type (17 bp, 241 bp, 268 bp DNA fragments), heterozygous mutant (17 bp, 241 bp, 268 bp, 509 bp DNA fragments) and homozygous mutant (17 bp, 509 bp DNA fragments) (Figure 2).

Statistical analysis

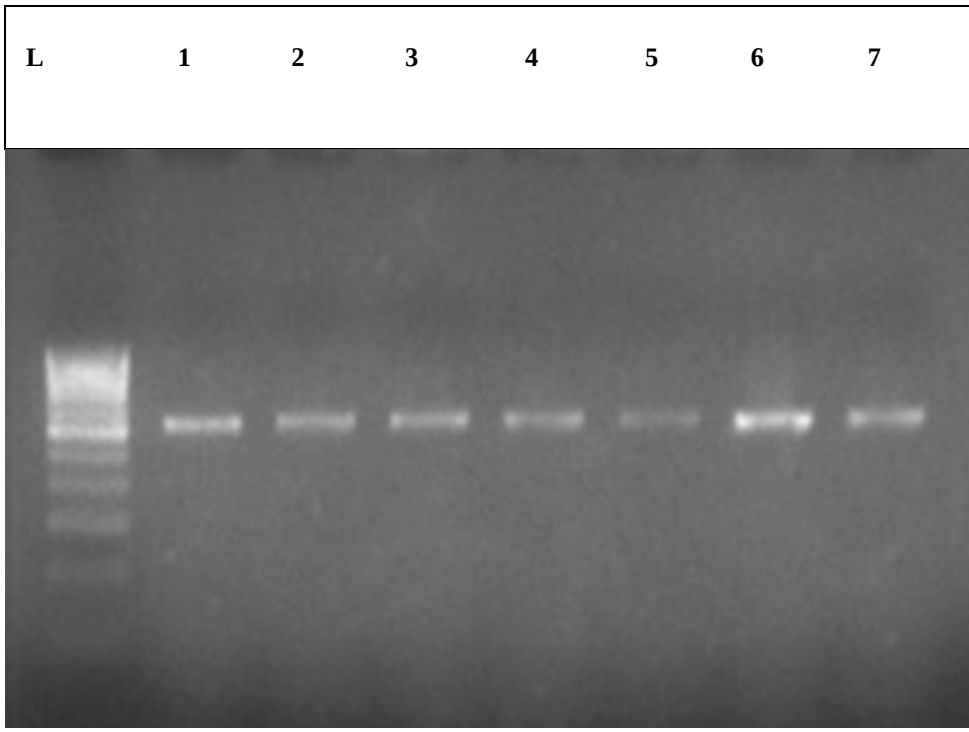
Data entry and analysis were performed using Epi-info (version 3.5.4 2012) software. Ink version 3.5.4 2012 and processed on Microsoft Excel 2013 software. The Student's T-test was used to compare the means between the different groups. A value of $p<0.001$ was considered statistically significant.

Ethical considerations

The study was approved by the Health Research Ethics Committee, deliberation No. 2019-3-037, under the dual supervision of the Ministry of Higher Education, Scientific Research and Innovation and the Ministry of Health. Permission to collect data was obtained from the Department of Defense and Veterans Affairs. All study patients consented to participate in the study. Data confidentiality was maintained throughout the study.

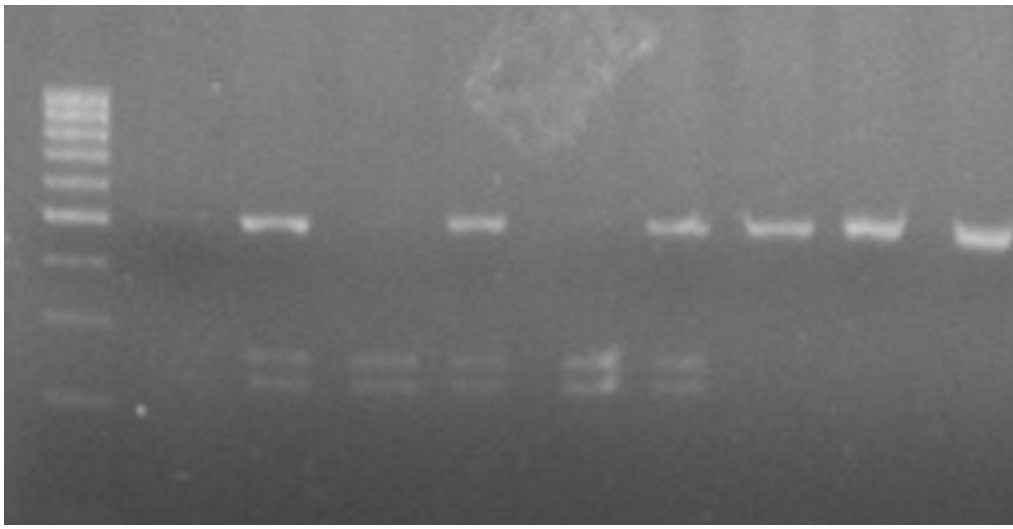
Table 1: The MIX PCR and digestion mix.

Reagents	**Volume used in a single reaction (in µL) PCR MIX**	**Volume used in a single reaction (µL) The digestion Mix**
5X GoTaq poly reaction buffer	5	
5mM dNTPs	0.625	
10µM CYP2B6-4F	1	
10µM CYP2B6-4R	1	
5U/µL GoTaq Flexi DNA pol	0.2	
Sterile distilled water (sdH_2O)	17.175 (Make up to 25 µL)	17.7(Make up to 30 µL)
PCR product		10
10X Buffer B		2
10U/µL BSeNI (or BsrI)		0.3
Total reaction volume	25	30



►526pb

Figure 1: PCR product on a 1.5% agarose gel stained with GRGreen (100 min, 100 V, 5 µL GeneRulerTM 100 bp DNA Ladder Plus) for quality control by visualization on a UV-doc system.



►509 pb
►268 bp
►241 pb

Figure 2: Genotyping of CYP2B6 variants by PCR-RFLP analyzed with 2,5% agarose gel electrophoresis: (a) shows the fragments after digestion with BSeNI (or BsrI) of the PCR product for identification of the CYP2B6 G 516 T variant.

RESULTS

Participants

During the study period, among patients enrolled, 61 changed treatments during their follow-up.

Sociodemographic parameters

The majority of our 155 patients were aged between 31 and 45 years old. The sex ratio (female/male) was 1.27, with 73 patients (47%) male and 82 patients (53%) female. The majority of patients were married (45.10%), followed by single people (26.10%) (Table 2).

CYP 2B6* 6 genotyping

HIV type 1 accounted for the majority of infections, with 94.2% of cases. Of 155 patients, 61 patients had changed treatment regimens at one time point for various reasons. The majority of the 61 patients, 32 patients, received an initial treatment regimen based on the AZT/3TC/NVP combination, followed by 18 patients of the TDF/3TC/EFV regimens (Table 3). Currently, the majority of patients (48) are receiving TDF/3TC/DTG regimens, while 11 patients are receiving TDF/3TC/EFV-based regimens (Table III). CYP2B6 516G>T was successfully genotyped in 61/61 (100%) of the enrolled study subjects (Figures 1 and 2). The distribution of the major allele CYP2B6*T was 68%, and the minor CYP2B6*G allele was 32%. The heterozygous and homozygous mutants were 31% for the GT genotype and 52,5% for the TT genotype (Table 4).

Table 2: Sociodemographic parameters.

Parameters	Number	Percentage (%)
Age range (years)		
18-30	27	17,4
31-45	63	**40,6**
46-60	58	37,4
60 et +	7	4,6
Total	155	100
Marital status		
Bachelor	41	26,5
Cohabitation	22	14,2
Divorced	7	4,5
Married	70	**45,1**
Widow (er)	15	9,7
Total	155	100
Sex		
Male	73	47
Female	82	53
Total	155	100

Table 3: Initial ARV regimen and current ARV regimen of 61 patients who switched treatment.

Initial Protocol	Patients	Percentage	Protocol in progress	Patients	Percentage
TDF/3TC/DTG	1	1,64%	ABC/3TC/ATV-r	1	1,64%
D4T/3TC/NVP	**1**	**1,64%**	ABC/3TC/DTG	1	1,64%
TDF/FTC/NVP	**1**	**1,64%**	AZT/3TC/DTG	1	1,64%
TDF/FTC/LPV-r	3	4,92%	TDF/FTC/ATV-r	1	1,64%
TDF/FTC/EFV	**4**	**6,56%**	TDF/FTC/EFV	3	4,92%
AZT/3TC/EFV	**6**	**9,84%**	TDF/3TC/EFV	8	13,11%
AZT/3TC/LPV-r	7	11,47%	TDF/3TC/DTG	46	75,41%
TDF/3TC/EFV	**8**	**13,11%**			
AZT/3TC/NVP	**30**	**49,18%**			
Total	61	100,00%	Total	61	100,00%

Table 4: CYP2B6 516G>T allele and genotype distribution.

CYP2B6 516G>T	HIV (n = 61)
GG/rapid (%)	10 (16,5)
GT/intermediate (%)	19 (31)
TT/poor (%)	32 (52,5)
Allele G (%)	39 (32)
Allele T (%)	83 (68)

DISCUSSION

National prevention strategies and programs do not respond holistically to the needs of young people in all their diversity. Globally, only one in three young people demonstrate accurate knowledge of HIV prevention. Access to comprehensive, high-quality, gender- and age-appropriate sexuality education programs, both in and out of school, urgently needs to be strengthened to ensure that young people have the knowledge they need to prevent new HIV infections (UNAIDS., 2017). The most representative age group is 31-45 years. This may be because patients in this age group are the most sexually active. Female sex was the most dominant at 53% versus 47% for men, with a sex ratio of 1.27 in favor of women. This may be explained by vulnerability, sociocultural constraints and physiological makeup that make women more likely to be exposed to HIV infection than men (UNAIDS, 2017). The results of this study are not comparable to statistics from Burkina Faso, which show that out of 3100 people declared HIV-positive during 2020, there were twice as many women as men (UNAIDS., 2021). This can be explained by the choice of population and location of the study. Married people represented 45.1% of our sample. However, a study in Gabon showed a predominance of singles, widowers, or divorces at 62% (Cisse et al., 2013). Sixty-one patients had a change in treatment regimen for various reasons (insomnia, weight loss, drowsiness, dizziness, etc.). Thirty-two of 61 patients were receiving triple therapy with nevirapine. Eighteen of 61 patients were receiving triple therapy with efavirenz. In the initial treatment, the molecules that contained 600 mg of efavirenz were AZT/3TC/EFV, TDF/3TC/EFV and TDF/FTC/EFV (table III). Genetic variability of CYP2B6 has been reported to be associated with significant interindividual variations in pharmacokinetics of several clinically important drugs (antiretroviral, anticancer, antidepressant, antimalarial drugs). Moreover, preliminary pharmacogenetic testing is highly recommended for patients on efavirenz therapy for proper therapeutic efficacy and for limitation of adverse reactions (Mangó et al., 2022). Neurological and neuropsychiatric reactions are the manifestations most frequently experienced by efavirenz-treated patients and range from transitory effects, such as nightmares, dizziness, insomnia, nervousness and lack of concentration, to more severe symptoms, including depression, suicidal ideation or even psychosis. Nevirapine (NVP) has been suggested to be an inducer of the CYPs responsible for its own metabolism, and hepatic CYP2B genes are considered the most inducible CYP isoforms13. CYP2B6 could play an important role in NVP metabolism (Yoon et al., 2020). Currently, the majority of patients, 48 patients, have benefited from a therapeutic regimen based on the TDF/3TC/DTG combination, followed by 11 patients of the TDF/3TC/EFV regimens with EFV 400 mg (Table III). In view of the difficulty of finding this molecule on a national level, these patients will soon switch to DTG. The 2018 WHO recommendations for the treatment of HIV-1 have placed dolutegravir-based therapies (DTGs) at the forefront of treatment, particularly in resource-limited countries. However, several studies have shown that Dolutegravir (DTG) is associated with significant weight gain, especially in women and black skin patients. In terms of tolerability, DTG is still associated with significant weight gain compared to Efavirenz (EFV) in naïve treatment HIV-1-infected patients in Cameroon. Although weight gain appears to stabilize over time, longer follow-up of patients on DTG is needed to assess long-term effects (Perrineau et al., 2020). The distribution of alleles and genotypes in different study groups is given in Table 4. This study results (GG: 16.4%; GT: 31.1% and TT: 52.5%) are significantly different from those obtained in a previous study concerning the Burkinabe population (GG: 31%; GT: 51% and TT: 18%) (P-value < 0.0001) (Karfo et al., 2023). The CYP2B6 516T allele remains a major allele in patients living with HIV followed at the Medical Center of Camp General Aboubacar Sangoule Lamizana for whom the treatment was changed after the initiation of treatment because of the appearance of side effects. The deficient

CYP2B6 516 T allele is associated with higher efavirenz plasma drug levels and more frequent Central Nervous Symptoms (CNS) -related symptoms (Gallien et al., 2017). Lin Cheng et al demonstrated that compared with the normal efavirenz clearance genotype CYP2B6-516 GG, the slow and very slow efavirenz clearance genotypes GT and TT were significantly associated with an increased risk of efavirenz-induced CNS side effects but not an increased virologic response. To promote the tolerance of efavirenz, it is better to adjust the dosage of efavirenz according to the polymorphisms of CYP2B6-516 in HIV-infected adults (Lin Cheng et al., 2020). This is the first meta-analysis evaluating the influence of CYP2B6 gene polymorphisms on NVP trough concentrations. HIV-infected patients with the CYP2B6 516TT genotype showed higher NVP concentrations than those with the GG or GT genotype. Notable statistical significance was also attained in each of the three respective comparisons of genotypes (Yoon et al., 2020).

Conclusion

The CYP2B6 516T allele remains a major allele in patients living with HIV followed at the Medical Center of Camp General Aboubacar Sangoule Lamizana for whom the treatment was changed after the initiation of treatment because of the appearance of side effects. It would be interesting to take into account the new recommendations for initiating ARV treatment to prevent side effects. Studies could be continued to set up cytochrome mutation detection kits to anticipate the onset of side effects and adapt treatments.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Conceptualization, data processing, formal analysis and software: RK, EK. Survey, methodology and project administration: RK and EK. Supervision, validation and visualisation: EK and JS. Writing - original version: RK. Drafting - revision and editing: RK, AK, AK, EK and JS.

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