



Genetic Diversity of N-Acetyl-Transferase II (NAT2) and Cytochrome P450 (CYP2C9) Polymorphisms in HIV/AIDS Seropositive Patients on Side Effects Due to Cotrimoxazole at the ALNADJAMA Multipurpose Center in N'Djamena, Chad

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Abstract

Introduction: Cotrimoxazole prophylaxis, an inexpensive and common intervention in developed countries, faces a lack of clear guidelines in resource-limited countries. The enzymes N-acetyltransferase 2 (NAT2) and cytochrome P450 (CYP2C9) influence Cotrimoxazole metabolism and side effects. This study explores the relationship between NAT2 and CYP2C9 polymorphisms and Cotrimoxazole side effects in HIV-positive patients in N'Djamena.

Methods: Blood samples were collected from 160 patients after consent, and DNA was extracted. NAT2 polymorphisms were detected by PCR-RFLP with the enzymes BamHI, KpnI, and Taq-1, while for CYP2C9, the enzyme BstNI was used.

Results: Of the 160 patients, 120 were taking Cotrimoxazole, with 49.07% (58/120) reporting side effects. Eight NAT2 genotypes were identified, with NAT2*4/6 predominating (25.9% of cases with side effects). Slow acetylators accounted for 44.8%. A significant association was observed between the NAT2*4/6 genotype and side effects (Odds ratio 1.030, p-value 0.053). CYP2C9*2 and CYP2C9*3 variants were uncommon (<4%). Most patients had wild-type or heterozygous phenotypes.

Conclusion: Cotrimoxazole side effects in HIV-positive patients are mainly associated with NAT2 polymorphism, in particular the NAT2*4/6 genotype. CYP2C9 variants do not appear to be significantly associated with adverse effects. These results underline the importance of continuing pharmacogenetic research to better identify predictive markers and improve prophylaxis in HIV-positive patients. A multi-genetic approach and clinical risk stratification are recommended.

Keywords: Ndjamen; Side Effects; Cotrimoxazole; N-acetyltransferase II; HIV; Acetylator; Chad; Cotrimoxazole; CYP2C9; HIV; Metaboliser

Introduction

HIV, a formidable retrovirus, attacks and destroys the immune system [1]. Currently, approximately 39.9 million people are living with HIV, resulting in 630,000 deaths from opportunistic infections [2]. The African region is the most affected, with 25.9 million people living with HIV in 2023 [2]. In Chad, the HIV prevalence rate is 1.1%. Despite international efforts, the fight against HIV/AIDS remains a major public health challenge, particularly in low- and middle-income countries. Advances in antiretroviral therapy and cotrimoxazole prophylaxis strategies have significantly improved the quality of life of people living with HIV. This prophylaxis has proven



to be a simple and effective intervention for reducing morbidity and mortality related to opportunistic infections [1]. Two enzymes, cytochrome CYP2C9 and N-acetyltransferase 2 (NAT2), play key roles in the metabolism of cotrimoxazole [3, 4]. Genetic variations in the genes encoding NAT2 and CYP2C9 can influence metabolic rates, resulting in rapid or slow acetylator phenotypes [4]. This genetic diversity significantly impacts the pharmacokinetics and pharmacodynamics of drugs. In particular, in the context of HIV/AIDS, CYP2C9 polymorphisms can lead to interindividual variations in cotrimoxazole metabolism, thus increasing the risk of side effects.

In Chad, few studies have examined the impact of NAT2 and CYP2C9 polymorphisms on cotrimoxazole tolerance in HIV-positive patients, thus limiting the possibility of personalizing treatments to reduce adverse effects. This study, conducted in N'Djamena, aims to explore NAT2 and CYP2C9 polymorphisms to predict side effects related to cotrimoxazole use in HIV-positive patients in Chad.

Materials and Methods

Study setting: The study was conducted at the AL NADJAMA Multipurpose Center in N'Djamena, Chad. The analyses were carried out at the Laboratory for Research in Biotechnology and Public Health (LAPHER-Biotech) of the Biotechnology Center at the University of Yaoundé 1.

Study type and period: This was a case-control study comparing the genotypes and phenotypes of patients receiving Cotrimoxazole prophylaxis who experienced side effects to those of patients without side effects. The study ran from May 4, 2022, to September 6, 2024.

Study population: The study population consisted of HIV-positive patients.

Selection criteria

- HIV-positive patients aged 18-60 years, on Cotrimoxazole, with a complete medical record and having signed the informed consent were included.
- HIV-positive patients under 18 and over 60 years of age, without Cotrimoxazole, and who had not signed informed consent were not included.

Sampling: Sampling was done by convenience and not by probability.

Data collection techniques: The HIV-positive patients receiving cotrimoxazole prophylaxis were interviewed. After providing informed consent, blood samples were taken. Medical records were reviewed to identify side effects related to cotrimoxazole.

Molecular analyses

DNA extraction: DNA was extracted using the Chelex-100 method. Filter papers containing blood spots were incubated with saponin, then treated with a Chelex-100 solution to extract the DNA, which was stored at -20°C for later analysis.

PCR amplification of the NAT2 and CYP2C9 genes: The NAT2 gene was amplified using NAT2F and NAT2R primers. The PCR protocol included initial denaturation at 95°C, followed by 30 amplification cycles and a final extension at 72°C. The PCR products were stored at 4°C. This was performed according to the protocol described by Zhi Yu *et al.*, [5] using CYP2C9F and CYP2C9R primers. The amplification program, pre-recorded in the thermocycler (T3 thermal cycler (Biometra, UK)), was carried out as follows: denaturation (94°C, 5 min) followed by 30 cycles of amplification (94°C, 30 s), hybridization (64.5°C, 30 s), and extension (72°C, 30 s). The final extension which occurs at the end of these cycles is carried out (at 72°C, 10 min).

RFLP (Restriction Fragment Length Polymorphism) Digestion of NAT2 and CYP2C9 PCR Products: The PCR products were digested with the restriction enzymes BamHI, KpnI, and Taqα-1. The mixtures were incubated at 37°C for BamHI and KpnI, and at 65°C for Taqα-1. The restriction enzyme BstNI was used for CYP2C9 gene digestion according to a protocol described [5]. Digestion was carried out in a 20 µl volume containing PCR water, buffer (10X buffer), 4 U/µl of BstNI restriction enzyme, and 8 µl of CYP2C9 amplicon. Digestion was performed in an incubator at 60°C for a minimum of 6 hours.

DNA fragment size determination: PCR and RFLP products were analyzed by 2% agarose gel electrophoresis. DNA fragments were visualized on a UV transilluminator.

Statistical analyses: The data were analyzed using Excel for means and standard deviations and SPSS for allele frequencies and correlation tests. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) were determined, with a *p*-value <0.05 considered statistically significant.

Ethical considerations: Ethical and administrative approval was obtained from the National Bioethics Committee of Chad, the University of N'Djamena, and the AL NADJAMA Multipurpose Center. Informed consent was obtained from the patients.

Results

Of the 160 patients surveyed, 120 were taking cotrimoxazole and 40 were not, representing 75% (120/160) of those taking cotrimoxazole and 25% (40/160) of those not taking it. Among those taking cotrimoxazole prophylaxis, 58 experienced side effects in combination with antiretrovirals, a rate of 48.33% (58/120),

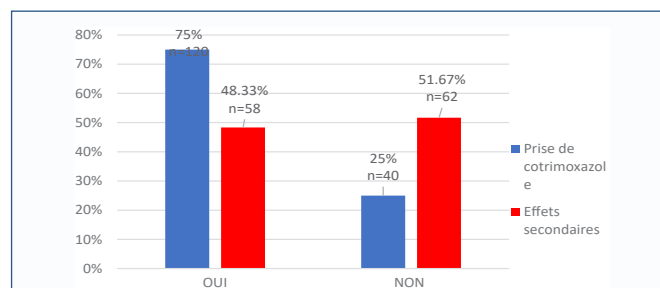


Figure 1: Distribution of patients according to cotrimoxazole intake and side effects.

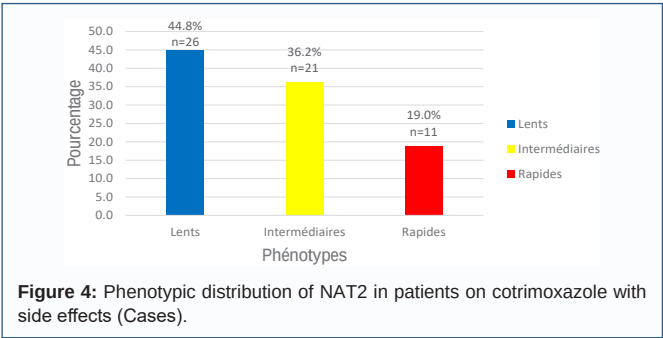
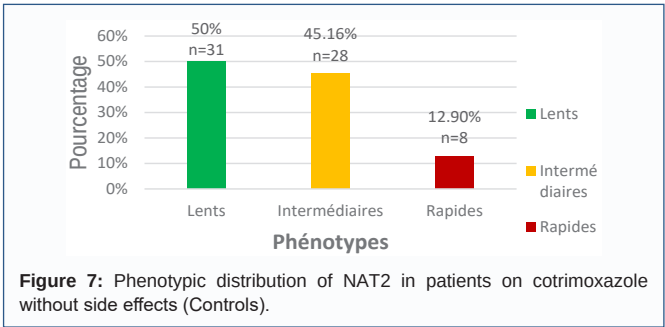
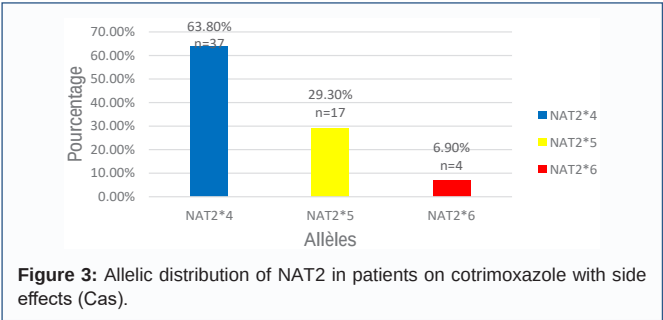
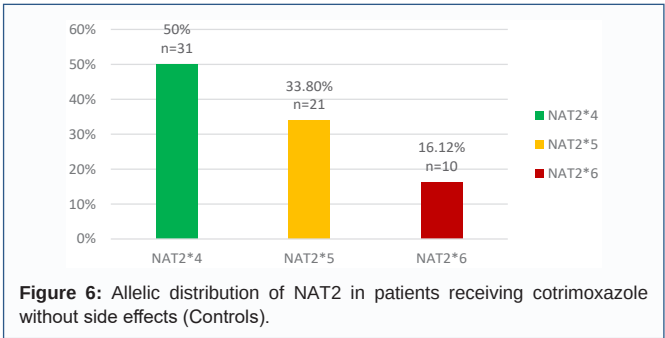
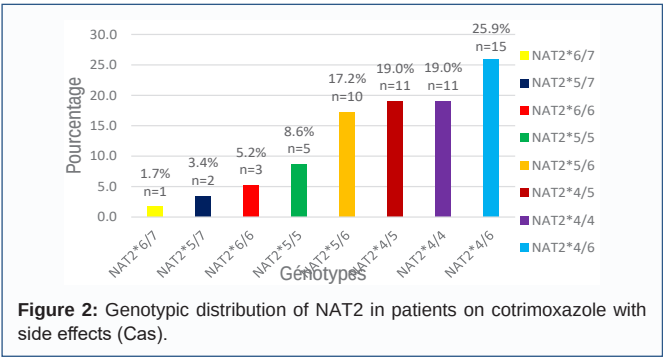
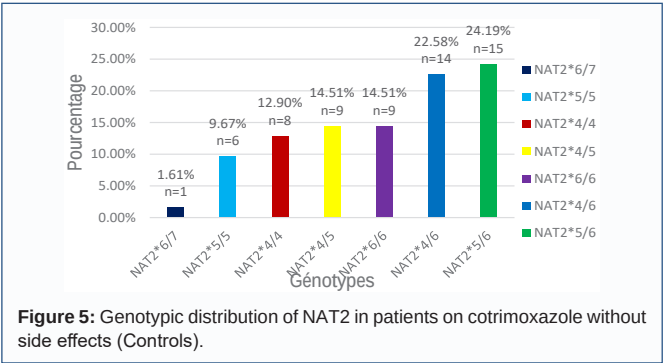


Table 1: Comparative table of the representation of genotypes of cases versus controls.

Genotypes	Patients with side effects	Patients without side effects	Total
NAT2*6/7	1	1	2 (1.7%)
NAT2*5/7	2	0	2 (1.7%)
NAT2*6/6	3	9	12 (10.0%)
NAT2*5/5	5	6	11 (9.2%)
NAT2*5/6	10	15	25 (20.8%)
NAT2*4/5	11	9	20 (16.6%)
NAT2*4/4	11	8	19 (15.8%)
NAT2*4/6	15	14	29 (24.2%)
Total	58	62	120 (100.0%)



compared to 51.67% (62/120) who did not experience any side effects (Figure 1 and 2).

Eight NAT2 genotypes were identified: NAT2* 4/4, NAT2* 4/5, NAT2* 4/6, NAT2* 5/5, NAT2* 5/6, NAT2* 5/7, NAT2* 6/6, and NAT2* 6/7. The NAT2*4/6 genotype was predominant, with a frequency of 15/58 (25.9%) among the patients (Figure 3).

Three groups of alleles were determined: the dominant allele was NAT2* 4 with 63.80% (37/58), followed by NAT2* 5 at 29.30% (17/58) and NAT2*6 at 6.90% (4/58) (Figure 4).

A phenotypic predominance of slow acetylators was observed,

with 44.8% (26/58) being slow acetylators exhibiting side effects to Cotrimoxazole, compared to 36.2% (21/58) of rapid acetylators and 19% (11/58) of intermediate acetylators (Figure 5).

Seven NAT2 genotypes were identified: NAT2* 4/4, NAT2* 4/5, NAT2* 4/6, NAT2* 5/5, NAT2* 5/6, NAT2* 6/6, and NAT2* 6/7. The NAT2*5/6 genotype predominated for the controls, with a frequency of 15/62 (24.19%) among the control patients (Figure 6).

Three groups of alleles were determined in the control patients: the dominant allele was NAT2* 4 with 50% (31/62), followed by NAT2* 5 at 33.80% (21/62) and NAT2*6 at 16.12% (10/62) (Figure 7).

A phenotypic predominance of slow acetylators was observed, with 50% (31/62) being slow acetylators exhibiting side effects to Cotrimoxazole, compared to 45.16% (28/62) of rapid acetylators and 12.90% (8/62) of intermediate acetylators.

Comparison of NAT2 genotypes of patients on cotrimoxazole with side effects versus those without side effects

Eight genotypes were observed in cases and seven in controls,

Table 2: Cross-tabulation between NAT2 alleles (cases and controls) and side effects due to cotrimoxazole.

ALLELES NAT2		Side effects YES NO		Total	Odd ratio	P-value	95% confidence
	Heterozygous	39 (67.2%)	40 (64.51%)	79 (65.8%)	1.03	0.05	0.805-1.317
	Homozygous	19 (32.8%)	22 (35.48%)	41 (34.2%)	0.94	0.48	0.595-1.506
Total		58 (100%)	62 (100%)	120 (100.0%)			

Table 3: Association between NAT2 phenotype (cases and controls) and side effects due to Cotrimoxazole.

PHENOTYPES NAT2		Side effects Yes No		Total	P-value	95% confidence
	Intermediaries	21 (26.2%)	21 (33.87%)	42 (35%)	0.96	0.782-0.932
	Slow	26 (44.8%)	31 (50.00%)	57 (47.5%)	0.66	0.585-0.739
	Fast	11 (19.0%)	10 (16.13%)	21 (17.5%)	1.45	0.850-1.936
Total		58 (100%)	62 (100%)	120 (100.0%)		

with a predominance of the NAT2*4/6 genotype in patients who developed side effects due to cotrimoxazole prophylaxis, with a proportion of 15/58, or 25.86%, in our case series. Whereas in the series of 62 patients without side effects due to cotrimoxazole (controls), patients with the genotypes NAT 2*5/6 were the most represented, with a slightly lower proportion of 15/62 (24.19%). Furthermore, no difference was observed between patients with the NAT2*6/7 and NAT2*5/7 genotypes in the general population (Table 1).

Association between NAT 2 alleles and the side effects of Cotrimoxazole

The table reveals a high rate of side effects among heterozygous patients, at 67.2% of cases, compared to 64.5% of controls. Furthermore, among homozygous patients, controls predominate over cases, at 35.48% *versus* 32.8%. Pearson's association test shows a significant association between heterozygous patients and side effects due to prophylactic cotrimoxazole use, with an odds ratio of 1.03 and a *p*-value of 0.05 at 95% confidence intervals (0.805-1.317). In contrast, the association is not significant for homozygous patients, with an odds ratio of 0.94 and a *p*-value of 0.48 at 95% confidence intervals (0.595-1.506) (Table 2).

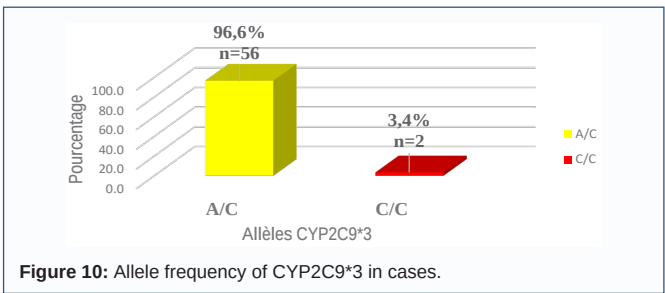
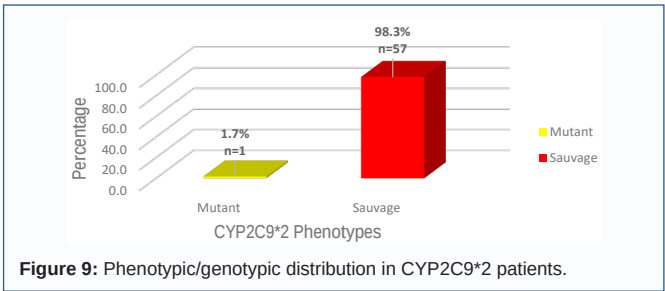
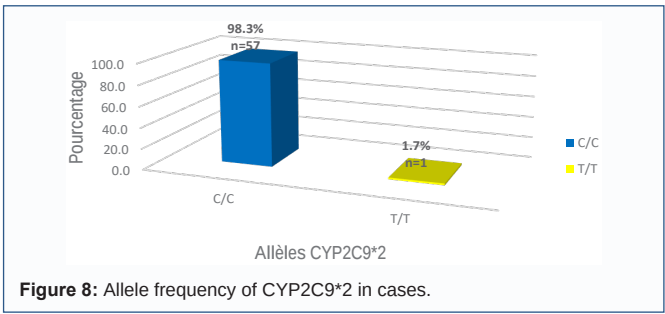
Association between NAT2 phenotypes (cases and controls) with the side effects of Cotrimoxazole

The table indicates a predominance of slow acetylators who developed side effects due to cotrimoxazole prophylaxis, with a proportion of 44.8% of cases versus 50% of controls, followed by intermediate acetylators at 26.2% versus 50% of controls. Conversely, rapid acetylators were the least represented in the case group, with a proportion of 19% compared to 16.13% in controls. Pearson's association test shows a non-significant association between these phenotypes and side effects due to cotrimoxazole prophylaxis, with a *p*-value of 0.662 within a 95% confidence interval (0.585-0.739) (Table 3).

Of the 160 patients surveyed, 120 were taking cotrimoxazole and 40 were not, representing 75% (120/160) of those taking cotrimoxazole and 25% (40/160) of those not taking it. Among those taking cotrimoxazole prophylaxis, 58 experienced side effects in combination with antiretrovirals, a rate of 48.33% (58/120), compared to 51.67% (62/120) who did not experience any side effects.

Allele frequency of CP2C9*2 in patients who experienced side effects from cotrimoxazole (Cas) (Figure 8)

For the observed allele frequencies for CYP2C9*2, the dominant allele in our study was C/C, corresponding to the genotype/phenotype of wild type, *i.e.*, a rate of 98.3% of customers and a minority of T/T



alleles designating customers of mutant types with a proportion of 1.7%.

Phenotypic frequency of CP2C9*2 in cases (Figure 9)

In subjects who experienced side effects from cotrimoxazole, the phenotypic frequency of sage-type patients predominated over mutants, representing 98.3% compared to 1.7% of mutant types.

CYP2C9*3 allele frequency in patients who experienced side effects from cotrimoxazole (Cas) (Figure 10)

In the cases for the allele frequency of CYP2C9*3, the dominant allele in our study series was A/C, corresponding to the genotype/phenotype of wild type, *i.e.*, a rate of 96.6% of clients and a minority of C/C allele designating clients of mutant type with a proportion of

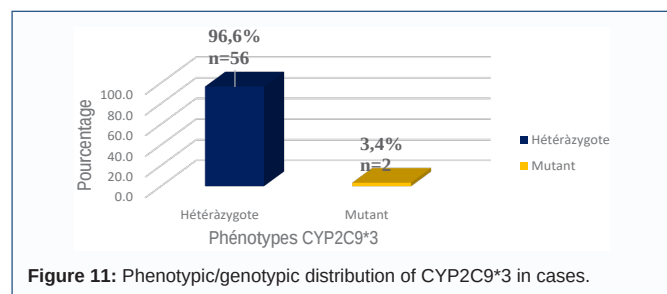


Figure 11: Phenotypic/genotypic distribution of CYP2C9*3 in cases.

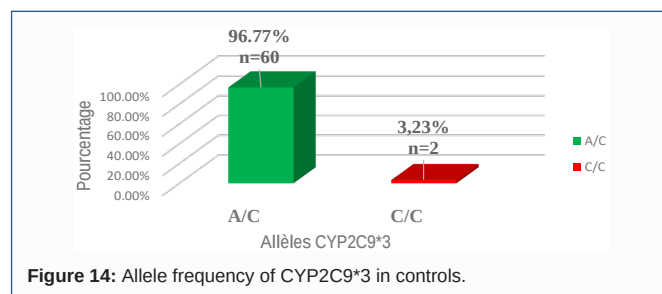


Figure 14: Allele frequency of CYP2C9*3 in controls.

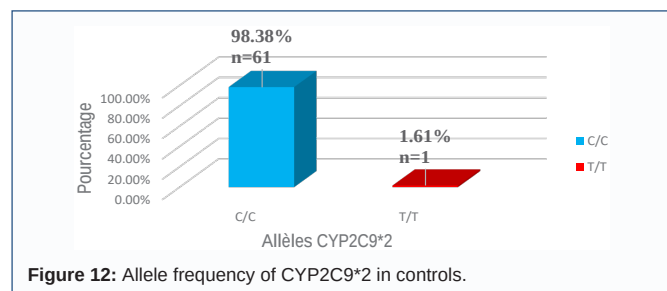


Figure 12: Allele frequency of CYP2C9*2 in controls.

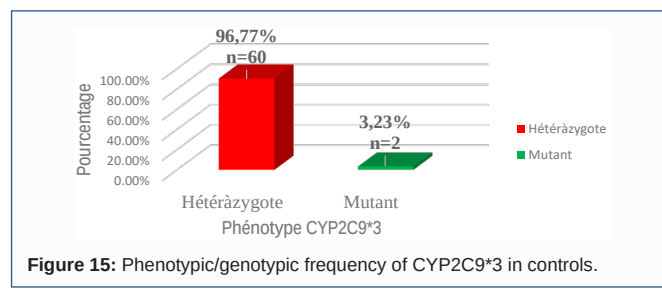


Figure 15: Phenotypic/genotypic frequency of CYP2C9*3 in controls.

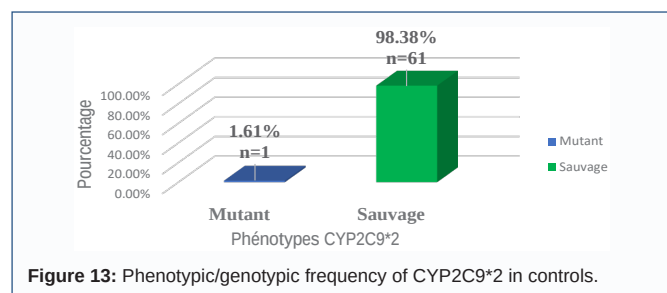


Figure 13: Phenotypic/genotypic frequency of CYP2C9*2 in controls.

3.4% having had side effects to cotrimoxazole.

Phenotypic/genotypic frequency of CYP2C9*3 in clients who experienced side effects from cotrimoxazole (Cas) (Figure 11)

Our study reveals a phenotypic predominance of heterozygous clients in the cases with a proportion of 96.6% compared to clients with the mutant phenotype which represents 3.4%.

CP2C9*2 allele frequency in customers who did not experience side effects from cotrimoxazole (Controls) (Figure 12)

The dominant allele in our study is A/C corresponding to the heterozygous genotype/phenotype, i.e., a rate of 98.38% of clients, 1.61% of allele C/C designating clients of mutant types.

Phenotypic/genotypic frequency of CP2C9*2 in controls (Figure 13)

In our study, there is a phenotypic predominance of wild type, i.e., a rate of 98.38% of clients and a minority of mutant types with a proportion of 1.61% of clients.

CP2C9*3 allelic frequency in patients without side effects from cotrimoxazole (Controls) (Figure 14)

For patients who did not experience side effects from taking cotrimoxazole prophylaxis, the dominant allele in our study was A/C corresponding to the heterozygous genotype/phenotype, i.e., a rate of 96.77% of clients, 3.23% of allele C/C designating clients of mutant types.

Phenotypic/genotypic frequency of CYP2C9*3 in controls (Figure 15)

Among subjects with the CYP2C9*3 phenotype in the control series, i.e., patients who did not experience side effects due to cotrimoxazole, we obtained a phenotypic predominance of heterozygotes, i.e., 96.77%, and a low proportion of mutants at 3.23%.

Discussion

This research, focusing on the study of NAT2 gene polymorphism to predict hypersensitivity in HIV-positive patients taking Cotrimoxazole in N'Djamena, identified eight NAT2 genotypes in the cases: NAT2* 4/4, NAT2* 4/5, NAT2* 4/6, NAT2* 5/5, NAT2* 5/6, NAT2* 5/7, NAT2* 6/6, and NAT2* 6/7. The NAT2* 4/6 genotype was predominant, with a frequency of 15/58 (25.9%). client's case and 15/62 (24.19%) among control clients. These results are similar to those obtained by Kengne *et al.*, [6] in Yaoundé, who identified nine genotypes with a predominance of NAT2* 4/6 (19%). However, our results differ from those of Pirmohamed *et al.*, [7] in Ethiopia, who identified five genotypes with a predominance of NAT2* 5/5 (48.5%). These results contrast with those of Mballa *et al.*, (2019) in northern Cameroon, where the NAT2* 5/6 genotype predominated at 28.12%. These differences can be attributed to the genetic and ethnic diversity of African populations.

In our study, the dominant allele was NAT2* 4 in both groups (cases and controls), with a rate of 63.80% (37/58) in cases and 50% (31/62) in controls. These results are slightly higher than those obtained by Kengne *et al.*, [6] in Yaoundé, who found a NAT2*4 allele predominance of 46%. Furthermore, our results are significantly higher than those obtained by Hermann *et al.*, (2021) in Cameroon, where the NAT2*4 allele rate was 15% in their study. Slow acetylators were predominant at 44.8% (26/58) with side effects due to cotrimoxazole (cases) and 50% in controls. Our results are lower than those obtained by Kengne *et al.*, [6] in Cameroon (54%) and significantly lower than those of Lin *et al.*, [8] in Singapore (58%). In contrast, Mballa *et al.*, (2019) obtained slow acetylator phenotypes at 61.4%, significantly higher than ours. The phenotypic frequency of slow acetylators in our study is also lower than that observed in Moroccans (over 90%) by Dandara *et al.*, [9] and in Hong Kong

(73%) by Magalon *et al.*, (2008), but significantly lower than those observed in Algeria (50%) by Khelil *et al.*, (2007).

Knowledge of patients' metabolic status is essential for understanding differences in treatment response between populations [10]. Our study in N'Djamena suggests that clinicians could consider treatments based on metabolic status to avoid hypersensitivity reactions and adverse effects. Indeed, previous studies have shown that a slow acetylator phenotype is an independent risk factor for adverse effects related to cotrimoxazole treatment compared to a rapid acetylator phenotype.

Our study also showed a weakly significant association between the NAT2*4/6 genotype (heterozygotes) and side effects from prophylactic cotrimoxazole use, with an odds ratio of 1.03 and a *p*-value of 0.05 at 95% confidence interval (0.805-1.317). In contrast, the association was not significant for homozygous clients, with an odds ratio of 0.94 and a *p*-value of 0.48 within a 95% confidence interval (0.595-1.506). These results are similar to those obtained by Marcus *et al.*, (2000) in the United States, where slow acetylators had an approximately 40% increased risk compared to rapid acetylators. However, they differ from the work of O'Neil *et al.*, [11], where the higher frequency of the slow acetylator phenotype in patients with a history of sulfonamide hypersensitivity did not appear to be explained by metabolic changes.

This study shows a non-significant relationship in the occurrence of adverse effects, with a higher incidence in slow acetylators than in rapid acetylators, with an odds ratio of 0.73 and a *p*-value of 0.42 within a 95% confidence interval (0.340-1.582). These results are similar to those of O'Neil *et al.*, [11], where the majority of patients with a history of hypersensitivity presented with the slow acetylator phenotype [12-32].

Conclusion

The NAT2* 4/6 genotype was predominant among the eight NAT2 genotypes identified in cases, while patients with NAT 2*5/6 genotypes were the most represented in controls. Heterozygous patients experienced more side effects from cotrimoxazole in cases than in controls. Patients with slow acetylator phenotypes experienced more side effects from cotrimoxazole in both cases and controls compared to rapid and intermediate acetylators. Pearson's association test shows that there is a weakly significant association in heterozygous clients with the NAT2*4/6 genotype (NAT2*4/NAT2*6) and slow phenotype with side effects due to taking cotrimoxazole prophylaxis with an odds ratio of 1.03, a *p*-value of 0.05 at 95% (0.805-1.317) and a non-significant association for homozygous clients with an odds ratio of 0.94 a *p*-value of 0.48 in a 95% confidence interval (0.595-1.506).

Analysis of the CYP2C9*2 allele frequency indicates that the wild-type allele, C/C, predominates in patients with side effects (98.3%), while T/T mutants account for only 1.7%. A similar trend is observed at the phenotypic level, where wild-type patients also represent 98.3%, suggesting that the majority of patients metabolize cotrimoxazole efficiently. This could explain why not all patients experienced side effects despite exposure to the drug.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

Authors' Contribution

MOF, WFM, CFT, and BBO contributed to the study design. MOF, CFT, and BBO coordinated the study. MOF, DT, AFO, and BBO supervised sample collection. CFT and MOF performed the molecular analysis. MOF, AAF, NN, and AFO performed the data analysis and interpretation. MOF, CFT, and NN drafted the manuscript. WFM and BBO critically reviewed the manuscript. All authors participated in the manuscript review and approved the final version before submission.

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Availability of Data and Materials

All data generated and/or analyzed during this study are included in this published article.

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