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Research Article

Genetic Diversity of Cytochrome P450 2C9 (CYP2C9) in HIV/AIDS Positive Patients Regarding Side Effects Induced by Cotrimoxazole at the ALNADJMA Multipurpose Center in N'Djamena, Chad

Moudiné Ouadjonré François [1,2*], Calvino Fomboh Tah [2], Faysala Oscar [1], Mahamat Nour Aguid Abakar [3], Ledjébaye Joseph [2], Brahim Boy Otchom [1], Wilfred Fon Mbacham [2]

[1] University of Ndjamena, Doctoral School-Technical Sciences and Environment, Doctoral Training, Biology and Human Health, Faculty of Health Sciences

[2] Laboratory of Research in Biotechnology and Public Health, Biotechnology Center (CBT) of the University of Yaoundé I

[3]Alnadjama Multipurpose Center

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*Address for Correspondence:

Moudiné Ouadjonré François, University of Ndjamena, Doctoral School-Technical Sciences and Environment, Doctoral Training, Biology and Human Health, Faculty of Human Health Sciences, LAPHER-Biotech, UYI BP: 1117 Ndjamena-Chad

Abstract

Introduction: HIV is a retrovirus that destroys the immune system. In Chad, HIV prevalence is 1.1%. Cotrimoxazole is a prophylactic drug that effectively reduces the morbidity associated with opportunistic infections. The genetic diversity of drug-metabolising enzymes, such as CYP2C9, influences the metabolism of cotrimoxazole in the occurrence of side effects. Although cotrimoxazole prophylaxis is common and cost-effective, clear guidelines are lacking in countries such as Chad. The aim of this study is to evaluate and compare CYP2C9 gene variants in HIV-positive patients at the Alnadjama centre and to analyse their impact on cotrimoxazole tolerance in order to support personalised therapeutic approaches.

Methods: A case-control study was conducted from May 2022 to September 2024 at the Alnadjama Multipurpose Center in N'Djamena, Chad, with molecular analyses performed at LAPHER-Biotech, University of Yaoundé I, Cameroon. HIV-positive patients aged 18–60 years on cotrimoxazole prophylaxis were divided into groups based on the presence or absence of side effects. After informed consent, interviews and blood samples were collected, and medical records reviewed. DNA was extracted using the Chelex-100 method, CYP2C9 gene amplified by PCR, digested with BstNI enzyme, and fragments analyzed by agarose gel electrophoresis. Statistical analyses included allele frequencies, Chi-square tests, odds ratios (OR), and 95% confidence intervals, with significance set at $p < 0.05$.

Results: Among 160 patients, 120 received cotrimoxazole, with 58 (48.3%) reporting side effects. The CYP2C9**2 wild-type genotype (C/C) predominated (98.3%), with the mutant (T/T) rare (1.7%), regardless of side effects. For CYP2C9**3, the heterozygous genotype (A/C) was most common (96.6–98.4%), and the mutant (C/C) was rare (1.6–3.4%), with no significant differences between groups. Association tests showed no significant correlation between CYP2C9*2 or *3 variants and cotrimoxazole adverse effects (OR near 1, p not significant).

Conclusion: CYP2C9*2 and *3 variants were not significantly associated with cotrimoxazole side effects in this HIV-positive cohort. The findings highlight the value of pharmacogenetics and recommend further research incorporating multiple genes and clinical factors to better predict adverse drug reactions in these patients.

Keywords: N'Djamena, Side effects, Cotrimoxazole, CYP2C9, HIV, Genetic diversity, Chad, Polymorphism.

INTRODUCTION

HIV is a retrovirus that attacks and destroys the immune system (WHO, 2019). Approximately 39.9 million people live with HIV, with 630,000 deaths related to opportunistic infections (UNAIDS, 2024). The WHO African region is the most affected, with 25.9 million people living with HIV in 2023 (UNAIDS, 2024). In Chad, the prevalence of HIV is 1.1% (Spectrum, 2022). Despite efforts, HIV/AIDS remains a major public health problem, especially in low- or middle-income countries. Advances in antiretroviral treatment and cotrimoxazole prophylaxis have improved the quality of life for people living with HIV. Cotrimoxazole prophylaxis is a simple and effective intervention to reduce morbidity and mortality from opportunistic infections (WHO, 2006). Enzymes like cytochrome P450 play crucial roles in the metabolism of cotrimoxazole (Harouna et *al.,* 2015; Butcher et *al.,* 2002). The genetic diversity of metabolizing enzymes, such as cytochrome P450 (CYP2C9), significantly influences the pharmacokinetics

and pharmacodynamics of drugs. In the context of HIV/AIDS, where cotrimoxazole is commonly used to prevent opportunistic infections, polymorphisms in CYP2C9 may contribute to interindividual variations in medication metabolism, thereby increasing the risk of side effects (Desta et *al.,* 2002).

In Chad, few studies have explored the impact of CYP2C9 polymorphisms on cotrimoxazole tolerance in HIV-positive patients. This gap limits the ability to personalize treatments and reduce side effects (Adebayo et *al.,* 2005). Our study assesses the prevalence of CYP2C9 gene polymorphisms in HIV/AIDS positive patients followed at the Alnadjama multipurpose center and analyzes the side effects of cotrimoxazole according to CYP2C9 genotypes, proposing recommendations for an individualized therapeutic approach based on pharmacogenetics.

MATERIALS AND METHODS

Study Setting: The study was conducted in N'Djamena, Chad, at the AL NADJAMA Multipurpose Center. The analyses were performed at the Laboratory of Research in Biotechnology and Public Health (LAPHER-Biotech) of the Biotechnology Center of the University of Yaoundé I in Cameroon.

Study Design and Period: This was a case-control study comparing genotypes and phenotypes of patients on cotrimoxazole prophylaxis with side effects to those of patients without side effects. The study was conducted 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 complete medical records and who signed informed consent were included.

- HIV-positive patients under 18 and over 60 years, not on cotrimoxazole, and those who did not sign informed consent were excluded.

Sampling: The sampling was performed conveniently and non-probabilistically.

Data Collection Techniques: HIV-positive patients on cotrimoxazole prophylaxis were interviewed. After informed consent, blood samples were taken. Medical records were checked 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 and then treated with a Chelex-100 solution to extract DNA, which was stored at -20°C for further analysis.

PCR Amplification of the CYP2C9 Gene: This was performed according to the protocol written by (ZhiYu et *al.,* 2014) using CYP2C9F and CYP2C9R primers. The amplification program pre-registered in the thermal cycler (T3 thermal cycler (Biometra, UK)) was as follows: denaturation (94 °C, 5 min) followed by 30 amplification cycles (94°C, 30s), annealing (64.5°C, 30s), elongation (72°C, 30s). The final extension performed at the end of these cycles was carried out (at 72°C, 10 min).

RFLP Digestion of CYP2C9 PCR Products: The restriction enzyme BstNI was used for digestion of the CYP2C9 gene according to a described protocol (ZhiYu et al., 2014). The digestion was conducted in a 20 µl volume containing PCR water, buffer (10X), 4 U/µl of the restriction enzyme BstNI and 8µl of CYP2C9 amplicon. The digestion was performed in an incubator at 60°C for at least 6 hours.

Determination of DNA Fragment Sizes: PCR and RFLP products were analyzed by electrophoresis on a 2% agarose gel. DNA fragments were visualized under a UV transilluminator.

Statistical Analyses: The data were analyzed with 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 patients.

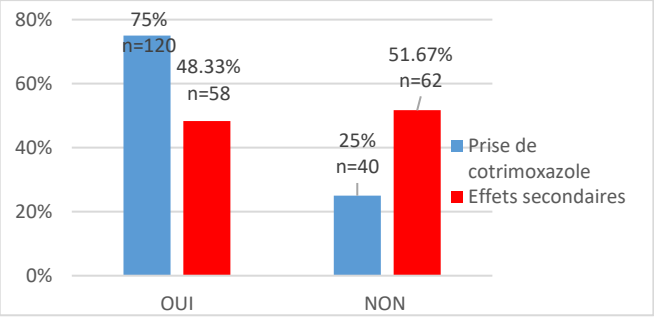

Figure 1: Distribution of Patients Based on Cotrimoxazole Use and Adverse Effects

Among the 160 patients surveyed, 120 were on Cotrimoxazole, and 40 were not, representing respectively 75% (120/160) on cotrimoxazole and 25% (40/160) of participants not on cotrimoxazole. Among those on cotrimoxazole prophylaxis, 58 reported adverse effects in association with antiretrovirals, yielding a rate of 48.33% (58/120), against 51.67% (62/120) who did not present adverse effects.

CYP2C9*2 Allele Frequency among Patients with Side Effects from Cotrimoxazole (Cases)

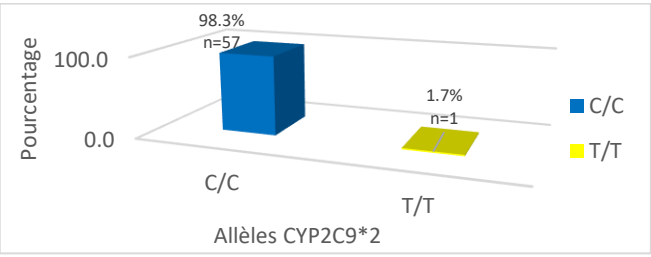

Figure 2: Allelic Frequency of CYP2C9*2 among Cases

For the observed allele frequency of CYP2C9*2, the dominant allele in our study was C/C, corresponding to the wild-type genotype/phenotype, indicating a rate of 98.3%, and a minority allele T/T represented patients with mutant types at a proportion of 1.7%.

Phenotypic Frequency of CYP2C9*2 among Cases

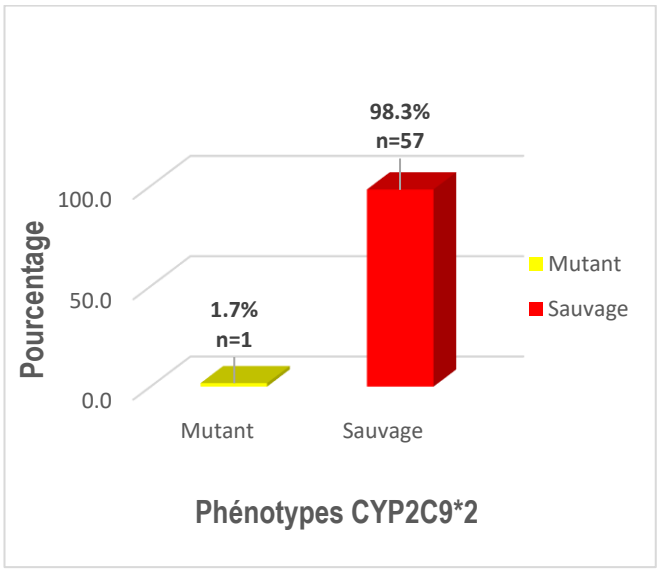

Figure 3: Phenotypic/Genotypic Distribution among CYP2C9*2 Patients

Among subjects with adverse effects from cotrimoxazole, the phenotypic frequency of wild-type patients predominated over mutants. A proportion of 98.3% versus 1.7% of mutant types.

CYP2C9*3 Allele Frequency among Patients with Side Effects from Cotrimoxazole (Cases)

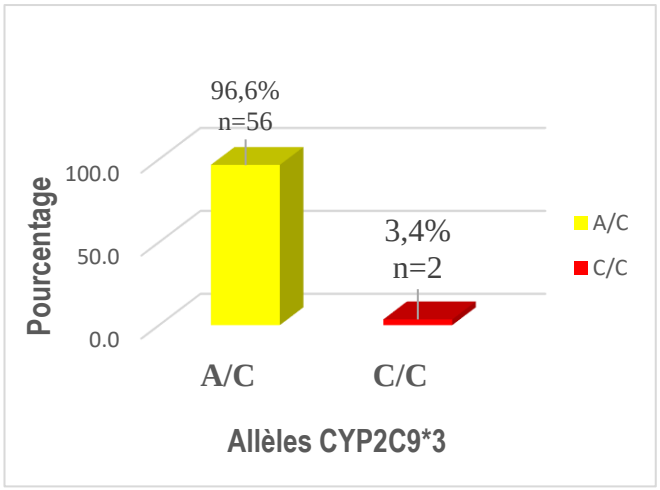

Figure 4: Allelic Frequency of CYP2C9*3 among Cases

In cases for the allelic frequency of CYP2C9*3, the dominant allele in our study was A/C, corresponding to the wild-type genotype/phenotype, indicating a rate of 96.6%, and a minority allele C/C represented patients with mutant types at a proportion of 3.4% who had side effects from cotrimoxazole.

Phenotypic/Genotypic Frequency of CYP2C9*3 among Patients with Side Effects from Cotrimoxazole (Cases)

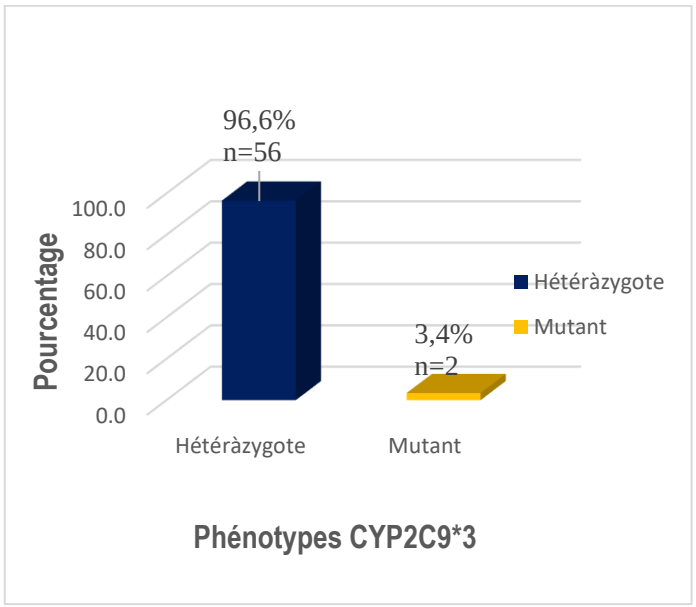

Figure 5 : Phenotypic/Genotypic Distribution of CYP2C9*3 among Cases

Our study reveals a phenotypic predominance of heterozygous clients among cases with a proportion of 96.6% relative to mutant phenotype clients representing 3.4%.

CYP2C9*2 Allele Frequency among Patients without Side Effects from Cotrimoxazole (Controls)

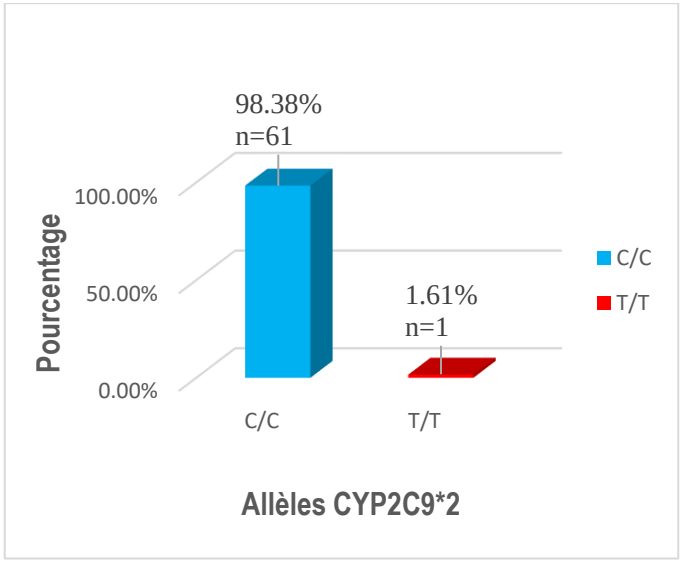

Figure 6: Allelic Frequency of CYP2C9*2 among Controls

The dominant allele in our study was A/C, corresponding to the heterozygous genotype/phenotype, indicating a rate of 98.38%, with 1.61% of alleles C/C representing patients with mutant types.

Phenotypic/Genotypic Frequency of CYP2C9*2 among Controls

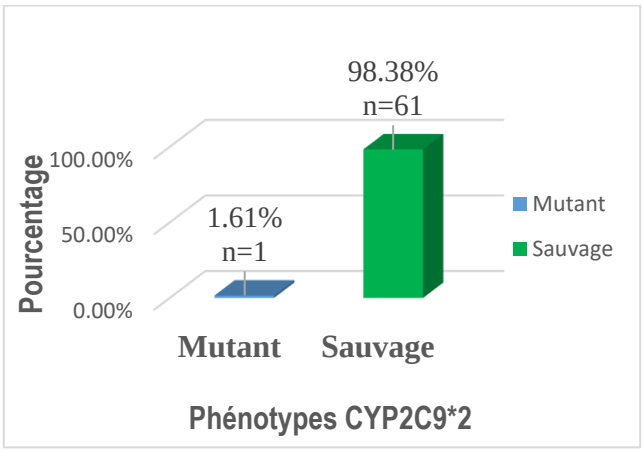

Figure 7: Phenotypic/Genotypic Frequency of CYP2C9*2 among Controls

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

CYP2C9*3 Allele Frequency among Patients without Side Effects from Cotrimoxazole (Controls)

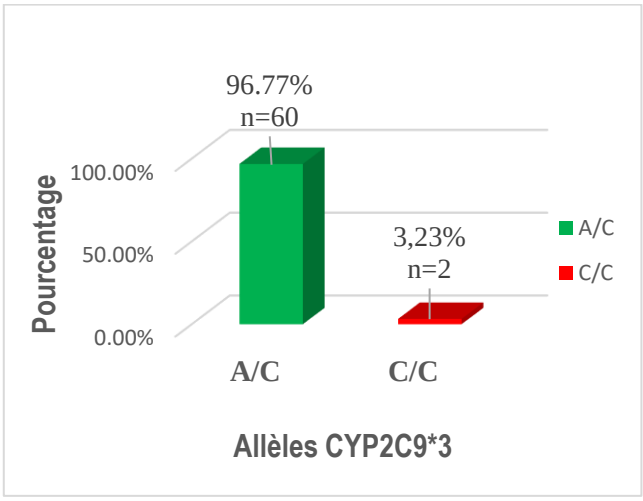

Figure 8: Allelic Frequency of CYP2C9*3 among Controls

For patients without side effects from cotrimoxazole prophylaxis, the dominant allele in our study was A/C, corresponding to the heterozygous genotype/ phenotype, indicating a rate of 96.77%, with 3.23% of alleles C/C representing patients with mutant types.

Phenotypic/Genotypic Frequency of CYP2C9*3 among Controls

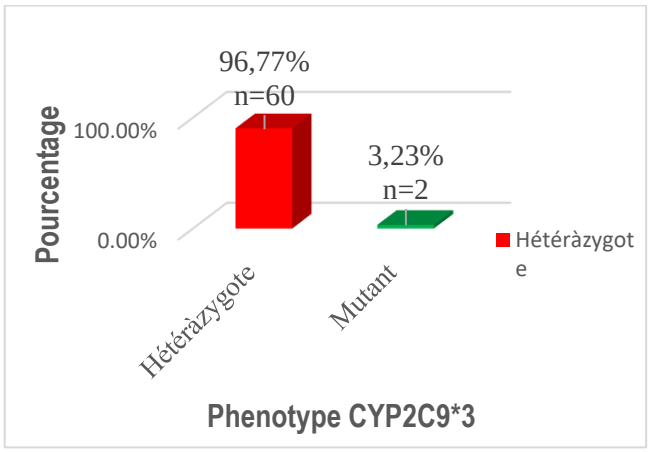

Figure 9: Phenotypic/Genotypic Frequency of CYP2C9*3 among Controls

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

Comparison of CYP2C9 Genotypes of Patients on Cotrimoxazole with Side Effects Against Those without Side Effects (Cases/Controls)

Our study involving 120 patients on cotrimoxazole, with 58 experiencing side effects referred to as "Cases" and 62 without side effects referred to as "Controls," revealed:

Two alleles were observed in cases for the CYP2C9*2 gene (C/C and T/T) with a predominance of the C/C allele representing the wild-type genotype/phenotype in patients who developed adverse effects due to cotrimoxazole prophylaxis at a rate of 98.3%, i.e., 57/58. For the CYP2C9*3 gene (C/C and A/C), the A/C allele predominated at 96.6%, representing the heterozygous genotype/phenotype.

In the controls for the CYP2C9*2 gene (C/C and T/T), two alleles were also found with a predominance of the C/C allele representing the wild-type genotype/phenotype in patients who did not develop adverse effects due to cotrimoxazole prophylaxis at a rate of 98.3%, i.e., 61/62. For the CYP2C9*3 gene (C/C and A/C), the A/C allele predominated at 96.7%, representing the heterozygous genotype/phenotype at 60/62.

In both cases, no significant differences were observed.

Table I: Comparative Table of Genotype Representation of Cases vs. Controls

			Cas (n=58)	Controls (n=62)	Total
Genotypes/ Phenotypes	**CYP2C9*2**	**C/C**	98,3% (57/58)	98,4% (61/62)	98,3%(118/120)
		T/T	1,7% (1/58)	1,6% (1/62)	1,7% (2/120)
	CYP2C9*3	**C/C**	3,4% (2/58)	2,3% (2/62)	3,3%(4/120)
		A/C	96,6% (56/58)	96,7% (60/62)	96,7%(116/120)

Association between CYP2C9*2 Phenotypes/ Genotypes and Side Effects of Cotrimoxazole

The Pearson association test (Chi-square) shows non-significant associations in patients with wild-type and mutant side effects with an Odds ratio of 0.934 and a p-value of 0.962 with a 95% confidence interval (0.239-3.912). Similarly, for the control group, the association was not significant for clients with wild-type and mutant phenotypes/genotypes, with an Odds ratio of 1.070 and a p-value of 0.735 in a 95% confidence interval (0.256-4.179).

Note: The odds ratio is calculated using the following formula: OR = AD/BC: 57x1/61x1 = 57/61 = 0.934.

Table II: Cross Table Between CYP2C9*2 Phenotypes (Cases and Controls) with Side Effects Due to Cotrimoxazole

		Phenotype CYP2C9*2					
		Sauvage	Mutant	Total	Odd ratio	p- value	IC à 95%
Effets secondaires cotrimoxazole	Cas	57	1	58	0,934	0,962	0,239 - 3,912
	Controls	61	1	62	1,070	0,735	0,256 - 4,179
Total		118	2	120			

Association between CYP2C9*3 Phenotypes/ Genotypes and Side Effects of Cotrimoxazole

The Pearson association test (Chi-square) shows non-significant associations in patients with heterozygous and mutant phenotypes/genotypes experiencing side effects from cotrimoxazole with an Odds ratio of 0.933 and a p-value of 0.946 with a 95% confidence interval (0.356-2.619). Likewise, for the control group, the association was not significant for clients with heterozygous and mutant phenotypes/genotypes, with an Odds ratio of 1.071 and a p-value of 0.735 in a 95% confidence interval (0.382-2.800).

Note: The odds ratio is calculated using the following formula: OR = AD/BC: 56x2/60x2 = 0.933.

Table III: Cross Table Between CYP2C9*3 Phenotypes/Genotypes (Cases and Controls) with Side Effects Due to Cotrimoxazole

		Phénotype CYP2C9*3					
		Heterozygous	Mutant	Total	Odd ratio	p- value	IC à 95%
Effets secondaires cotrimoxazole	Cas	56	2	58	0,933	0,946	0,356- 2,619
	Controls	60	2	62	1,071	0,735	0,382- 2,800
Total		**116**	**4**	**120**			

DISCUSION

In our study, out of 160 patients, 120 (75%) were on Cotrimoxazole, while 40 (25%) were not receiving this treatment. This distribution highlights the widespread use of Cotrimoxazole prophylaxis among patients, likely due to its recognized efficacy in preventing opportunistic infections, particularly in people living with HIV (Church et al., 2015; WHO, 2014).

It is also important to note that among the 120 patients on Cotrimoxazole, 58 (48.33%) reported adverse effects in association with antiretrovirals. This rateof adverse effects is concerning, indicating that nearly half of the patients on treatment may experience undesirable reactions. This underscores the need for increased vigilance in managing combination therapy in these patients, as highlighted in other studies (Delmas et al., 2011).

Analysis of the allelic frequency of CYP2C9*2 indicates that the wild-type allele, C/C, predominates among patients with adverse effects (98.3%), while mutant T/T accounts for only 1.7%. A similar trend is also observed at the phenotypic level, where wild-type patients also represent 98.3%, suggesting that the majority metabolize Cotrimoxazole effectively. This could explain why not all patients experienced side effects despite exposure to the medication.

Regarding the CYP2C9*3 polymorphism, the dominant allele was A/C (96.6%), with a minority (3.4%) of alleles C/C. The importance of these genetic variations lies in their potential to influence drug response and therefore contribute to the risk of adverse effects. The predominance of heterozygous patients suggests the possibility of variable responses within this population, justifying further studies on drug metabolism in African populations (Adebayo et al., 2005).

When comparing cases to controls (patients without side effects from Cotrimoxazole), the results show that allele A/C is likewise dominant, indicating that genetic

variation may also play a role in susceptibility to adverse effects. The phenotypic and genotypic frequencies for CYP2C9*2 in the controls reveal a distribution similar to that observed in the cases, with 98.38% being wild-type and 1.61% being mutants. This could suggest that, even in the absence of side effects, the majority of the population expresses the wild-type genotype.

Clinically, this study regarding the prevalence of CYP2C9 polymorphisms in the studied population provides important insights into the pharmacogenetics of treatments. Variations in allele frequency and the associated side effects of Cotrimoxazole highlight the importance of a personalized approach in treating patients living with HIV/AIDS (Pirmohamed et al., 2000).

Understanding CYP2C9 variants could help optimize drug choice and dosing to minimize side effects and improve adherence to therapy (Evans & Relling, 1999). Integrating genetic polymorphism screening into clinical practice could have beneficial implications for managing antiretroviral therapy in this population.

CONCLUSION

In conclusion, these findings emphasize the importance of pharmacogenetics in evaluating side effects of prophylactic treatments such as Cotrimoxazole. The data collected in our study can serve as a foundation for future research and assist in guiding therapeutic strategies to improve the management of patients living with HIV. Although the studied CYP2C9 variants do not appear to be predominantly associated with adverse effects from cotrimoxazole in this study, these results underscore the importance of continuing pharmacogenetic research to identify robust predictive markers. A multi-gene approach and stratification of clinical risk factors (e.g., immunological status, comorbidities) would be essential to optimize prophylaxis among HIV-positive patients.

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Conflicts of interest: The authors declare no conflict of interest.

Author's Contribution:

MOF, WFM, CFT, BBO contributed to the design of the study. MOF, CFT, BBO, coordinated the study. MOF, DT, AFO, BBO supervised the sample collection. CFT, LFA, DN, NKK, MOF performed the molecular analysis. MOF, MNAA, performed data analysis and interpretation. MOF, CFT wrote the manuscript. BBO, WFM critically revised the manuscript. All authors contributed in the revision of the manuscript and approved the final version of the manuscript prior to 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.

Limitations of the study: Insufficient data in the sub-Saharan African sub-region; insufficient financial means to reach all provinces of Chad.

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