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MECHANISMS OF DRUG RESISTANCE IN Plasmodium falciparum

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Abstract

Prevention, treatment and control of malaria mainly depends on the utilisation of synthetic drugs, unfortunately the parasites have developed resistance to almost all recommended drugs. Therefore, the aim of this paper was to review the state of knowledge on various resistance mechanism developed by Plasmodium falciparum. Antimalarial resistance is driven by a range of mechanisms, including molecular, genetic, and evolutionary factors. For Chloroquine, beside some basic molecular mutations, the parasite tends to divert the drug to enter the parasite's food vacuole rather than its specific target organelles of action. High-level resistance to Pyrimethamine is caused by mutations in the DHFR gene, particularly at codons 108, 59, 51, and 164, leading to variations such as Ser108Asn, Cys59Arg, Asn51Ile, and Ile164Leu. Mutations in the DHPS gene that reduce the effectiveness of Sulfadoxine include codon changes such as A437G/K540E and A437G/A581G. Mutations in the Kelch13 (K13) propeller domain are linked to slower parasite clearance, where C580Y mutation is the most common but several other mutations in or near the K13 region, such as N458Y, Y493H, R539T, and I543T are also attributed to artemisinin resistance. Anti-malarial drugs resistance surveillance should be strategically adopted in all malaria endemic region to monitor the emergence of resistance.

Keywords: *Plasmodium falciparum, Resistance, Mutations, Quinoloine, Antifolate, Artemisinin*

1.0 Introduction

Malaria is a vector- borne parasitic disease that is transmitted through the bite of an infected female anopheles mosquito that injects saliva harbouring the sprozoite stage of the parasite which move directly into the liver of the host. Five species of the parasites in the genus *Plasmodium* are responsible for human malaria (*P. falciparum, P.vivax, P .ovale, P. malariae, and P. knowlesi*) (Kumar and Mahato 2024). Two of the most prevalent signs of malaria are fever and chills, which are brought on by the body's immune system reacting to the parasite's antigens. Additional symptoms include extravascular hemolysis (produced by the sequestration of both parasitized and non-parasitized red blood cells) and anemia (induced by the intravascular rupture of the red blood cell). Due to their weakened immune systems, children under five years old and pregnant women are particularly susceptible to the disease. The disease continues to be one of the main causes of death in third-world countries. In 2017, the World Health Organization (WHO) estimated that there were 219 million cases of malaria world- wide, an increase of 2 million from the previous year, and as a result there were 435,000 deaths, which translate to 1190 per day, mostly young children (Tse, Korsik, and Todd 2019). Prevention and treatment of the disease rely mainly on the use of synthetic drugs. Several researches has shown that the parasites have developed resistance to almost all recommended drugs for treating the disease. For example Chloroquine which was considered as the most effective drug was lost to resistant for the past four-five decades (Manata et al. 2024).

Drug-resistant parasites emerged in Africa far later than in Asian countries, which is regarded as an epicentre of antimalarial drug resistance (Cassiano *et al*., 2024). For chloroquine, there is evidence of this reverse migration (when compared to the evolutionary genesis and expansion of *P. falciparum*) (Oboh *et al*., 2018). The emergence of resistance, particularly in *P. falciparum*, has been a major contributor to the global revival of malaria in the last three decades. Resistance is the most likely explanation for doubling of malaria-attributable child mortality in eastern and southern Africa. (White 2004). The advent of parasites resistant to chloroquine in the late 1950s and to most recently recommended

drugs like Sulphadoxine- Pyramethamine highlighted the need for novel antimalarial drugs. (Olanlokun *et al.*, 2024). Malaria drug resistance mechanisms are unusual, since the parasite is capable of producing resistance in the exact cellular target of the medication, drug resistance phenotype is typically created due to increased and non-specific efflux of pharmaceuticals through induction of Multidrug Resistance (MDR) transporters (Shibeshi, Kifle, and Atnafie 2020). MDR transporters are not the main mechanism of resistance in malaria; instead, most of the known mechanisms by which *P. falciparum* acquires resistance to antimalarial medications are connected to alterations in the parasite genome, such as single nucleotide polymorphisms (Pierreux *et al*., 2024). Therefore, the aim of this paper was to critically review various mechanism of resistance in *Plasmodium falciparum.*

2.0 MATERIALS AND METHODS

2.1 Literature Search

In order to obtain reliable and authentic research and published articles on the topic the following data bases were visited; PubMed,Web of Knowledge, EMBASE, Web of Science, Scopus, Google scholar, World Health Organization's WHOLIS and Medline. In addition Sci.Hub. was used to access some publications that were very difficult to access with the other data bases.

2.2 Search terms used

Search terms that were directly or indirectly linked to Antimalarial drugs resistance were used in order to generate relevant research papers. The following search terms were specifically used; Antimalarial drugs resistance, resistance to Quinolines, resistance to Chloroquine, resistance to Sulphadoxine-Pyrimethamine, resistance to Quinine, resistance to Mefloquine resistance to Artemisinins, Primaquine,, Hypnozoiticides, types of resistance. All research papers generated were carefully and critically analysed and scrutinised, after which the papers were grouped and classified based on the various headings and subheadings of the title of this of this paper.

3.0 RESULT AND DISCUSSION

3.1 Anti-malarial Drug Resistance

The World Health Organization (WHO) defines anti-malarial drug resistance as a situation where a strain of parasite can continue to survive and multiply even when treated with medication at doses that are equal to or higher than those usually recommended. This definition was later modified to include the sentence: "The form of the drug active against the parasite must be able to gain access to the parasite or the infected erythrocyte for the duration of the time necessary for its normal action" (Bakari *et al*., 2024). This resistance can occur as long as the person's body can handle the medication and the drug reaches the right level at the infection site. Resistance to antimalarial drugs arises because parasites with genetic mutations that reduce their susceptibility are selected and thrive. (Shibeshi, Kifle, and Atnafie 2020). Resistance to antimalarial drugs primarily occurs in *P. falciparum* and *P. vivax* and is mainly driven by mutations in drug-resistant genes or an increase in the number of these gene copies. (Menard and Dondorp, 2017). Resistance in *P. vivax* has been observed against CQ, primaquine, and antifolate drugs in many endemic regions. In contrast, *P. falciparum* has shown resistance to nearly all types of antimalarial treatments, including quinolines, antifolate drugs, and ART derivatives (Bansal *et al.*, 2017; Haldar *et al.*, 2018; Price *et al.*, 2014).

Antimalarial drugs have been vital in combating malaria, offering life-saving treatment and prevention to millions. However, the rise and spread of drug resistance are progressively weakening the effectiveness of these treatments, including artemisinin-based combination therapies (ACTs) (Mu, 2010). Managing drug-resistant malaria has become a major challenge (Farooq and Mahajan 2004). Identifying resistance to antimalarial medications has been a persistent challenge in malaria treatment globally (Fitri *et al*., 2023).

3.2 Types of Resistance in *Plasmodium falciparum*

Drug resistance is categorized into three types: These include; Receptor Interacting Protein type one (RI), Receptor Interacting Protein type two (RII), and Receptor Interacting Protein type three (RIII). Receptor Interacting Protein type one (RI) is characterized by initial effectiveness of the drug, followed by recurrence of the parasite load within a month of commencement of treatment. On the other hand, in RII cases, there is a decline in the parasite density following therapy but not complete clearance of the parasite as the parasitemia density rises again at some time later. RIII is the most severe type; here, the parasites exhibit minimum variation to the treatments administered. (Ismail, et.al., 2019)

3.3 Causes of Resistance in *Plasmodium falciparum*

Resistance appears to stem from changes in the structure, function, or quantity of proteins. Genetic modifications, like Single Nucleotide Polymorphisms (SNPs), drive these protein alterations. Researchers are continuously seeking solutions to the growing problem of antimalarial drug resistance, which is becoming the most significant barrier to effective antimalarial treatment. Resistant parasite strains will persist, making the continuous development of new compounds essential. New drugs with novel mechanisms of action are currently undergoing testing in clinical trials. (Shibeshi, Kifle, and Atnafie 2020).

Factors that result in the development and worsening of true resistance include, but are not limited to drug abuse, wrong drug administration, and administration of substandard drugs, interaction between the drugs, weak absorption, and incorrect diagnoses. These can all contribute to either the actual or perceived failure of treatment in a patient and also elevate the chances of exposing parasites to suboptimal drug concentrations. (Bloland, 2001).

4.0 MECHANISM OF DRUG RESISTANCE

Antimalarial resistance is driven by a range of mechanisms, including molecular, genetic, and evolutionary factors. (Usoro *et al*., 2024). Malaria parasites are able to develop resistance mainly because there's a high number of parasites in the bloodstream during the infection's asexual stage, combined with their ability to quickly change their genetic makeup. Resistance can come from various sources, such as random mutations, how the drugs interact with the parasites, the properties of the medications, and factors related to the human host, the parasites, the mosquito vector, and the environment. (Abdel Muhsin and Mackinnon *et al*., 2003). The

development and spread of drug-resistant Plasmodium species are closely tied to the different forms the parasite takes and the range of places it inhabits. This includes human liver cells, red blood cells, and also the midgut and salivary glands of mosquitoes (Blasco *et al*., 2017). For drug resistance to spread through the malaria parasite population, mutant parasites must successfully complete two critical stages of their lifecycle: gametocytogenesis and sporogony. Just as mutations in the *Plasmodium* cytochrome b complex that confer resistance to atovaquone seem to make the parasite transmissible, mutations that disrupt these key processes will spread slowly or not at all (Goodman *et al*., 2016). Malaria parasites employ resistance mechanisms similar to those seen in other microorganisms, such as drug efflux, changes to the drug target, and drug modification. Additionally, they use fewer common mechanisms related to their lifecycle and metabolic processes (Mbengue *et al*., 2015). Mutations in pfk13, for example, extend the parasite's duration in the earlier, less drug-sensitive ring stage and enhance the unfolded protein response. This prolongs the parasite's exposure to artemisinin, allowing the drug to be swiftly cleared and any damage caused by the drug to be repaired, effectively halting the parasite's development (Ippolito *et al*., 2021).

4.1 Mechanism of resistance to Quinolines (Chloroquine)

Chloroquine became a leading antimalarial drug for first-line treatment, shortly after the World War II. However, resistance in *P. falciparum* to Chloroquine was first detected in the late 1950s and quickly spread globally, leading to the development of new drugs and the eventual emergence of more expensive artemisinin-based combination therapies (ACTs). Early genetic studies indicated that the *pfcrt* gene was crucial for Chloroquine resistance in *P. falciparum*, and its role was confirmed through reverse genetics. Despite being the first-line treatment, Chloroquine resistance has also developed in *P. vivax*. (Kumar and Mahato 2024).

By the 1980s, Chloroquine resistance had become a significant global issue. The situation has worsened to the point where even in Central America, where chloroquine was once considered effective, the malaria parasites now show signs of resistance (Bhattacharjee and Shivaprakash 2016). Clinical resistance means the treatment isn't working as it should. If a patient still has or gets parasites back in their blood after treatment, or if parasites show up again in blood tests along with symptoms, it's a sign of resistance (WHO 2003). Since it's hard to tell if treatment has failed or if a new infection has occurred especially with multiple parasite strains and often low parasite counts in recurring cases, it is important to confirm treatment failure by matching the parasite strains from both the original and the new infection. (WHO 2007).

Chloroquine, which was once a widely used and effective antimalarial medication, has faced extensive resistance in Africa, making it ineffective for the treatment of the disease (Usoro *et al*., 2024). Chloroquine-resistant *P. falciparum* malaria is commonly reported in areas where falciparum malaria is endemic, except for Central America, the Caribbean Island of Hispaniola, and specific regions in the Middle East and Central Asia. This resistance often makes treatment more challenging, less affordable, and less safe (Farooq and Mahajan 2004). From the 1940s until the late 1980s, Chloroquine was the preferred antimalarial drug because of its cost, safety, and effectiveness. Resistance to Chloroquine emerged in at least four distinct regions: twice in South America, once in Southeast Asia, and once in Papua New Guinea. Despite widespread use, resistance developed slowly over nearly 20 years, suggesting that multiple genetic changes were required to produce this resistant strain. Even though chloroquine's effectiveness has waned, it is still in use for treatment of malaria in many areas unofficially, where the disease is common. However, the rise of chloroquine-resistant *P. falciparum* is linked to higher death rates and more cases of gametocytaemia (parasites in the blood) after treatment. There is also growing worry about the development of chloroquine-resistant strains and those resistant to Pyrimethamine/Sulfadoxine, especially in cases of uncomplicated *P. falciparum* malaria (Upadhyay 2016).

The exact mechanism of Chloroquine resistance remains unclear, but one theory suggests it may be related to the drug's ability to enter the parasite's food vacuole rather than its specific mode of action (Saifi et al. 2013). Parasites that are Chlroquine-resistant show reduced accumulation of Chloroquine in the digestive vacuole, a process driven by an energy-dependent mechanism that pumps the drug out (Wicht, Mok, and Fidock 2020). Consequently, chloroquine-resistant parasites can actively transport chloroquine out of the cell, suggesting that mutant and normal PfCRT proteins have different abilities to handle the drug (Shibeshi, Kifle, and Atnafie 2020).

Mutations in the PfCRT, which is responsible for a protein in the digestive vacuole membrane, are associated with chloroquine resistance. These mutations do not affect Chloroquine's interaction with heme or its target. Instead, chloroquine's resistance mechanism involves its interference with heme breakdown, which normally occurs through glutathione (GSH). Glutathione plays a key role in protecting cells by managing oxidative stress. The PfCRT protein helps transport peptides from the parasite's digestive vacuole into the cytosol, providing necessary amino acids and reducing osmotic stress. Mutations in PfCRT are linked to chloroquine resistance in malaria parasites. When comparing *P. falciparum* strains HB3 and Dd2, a 45-kDa protein with ten transmembrane domains was identified on chromosome 7. Analysis revealed eight different codon in PfCRT, with position 76, which changes lysine to threonine, being the most reliable marker for resistance, based on studies of various chloroquine-sensitive and resistant clones from different regions (Kumar and Mahato 2024).

Research has shown that the wild-type PfMDR1 protein is capable of transporting quinine and chloroquine but not halofantrine. In contrast, the mutant PfMDR1 protein can transport halofantrine but does not transport quinine or chloroquine (Sanchez et al 2008).

Moreover, multiple genetic changes drive chloroquine resistance. Key players include two genes: the P. falciparum multi-drug resistance-1 gene (Pfmdr1) on chromosome 5, which encodes the Pgh1 protein, and the chloroquine resistance transporter gene (Pfcrt) on chromosome 7, which produces the CQ resistance transporter protein. These genes are crucial in the rise of chloroquine resistance (Wahib *et al*.,2012).

To understand how drug resistance manifests in parasites, it's crucial to test their sensitivity in the lab using cultures grown from patient samples. However, this type of testing isn't typically

included in standard clinical care and is often not easily accessible, as it often requires specialized tests for each specific drug (Duru *et al*., 2015, Witkowski *et al*., 2015). Genotyping parasites for genetic markers of resistance is the third, most efficient method for tracking drug resistance. It kicks in once we've linked specific gene mutations to drug resistance and confirmed them in parasites collected from real-world situations (Prosser *et al*., 2014).

4.2 Mechanism of Resistance to Antifolates

Antifolate antimalarial drugs include proguanil, pyrimethamine, trimethoprim, sulfadoxine, and sulfamethoxazole (Cowel and Winzeler 2019). In Indonesia, antifolates are used in combination therapies like atovaquone-proguanil for prevention, especially for pregnant women and children, and sulfadoxine-pyrimethamine for treating *P. falciparum* (Bazie et al, 2020). Sulfadoxine, a para-aminobenzoic acid (pABA) lookalike, slams the dihydropteroate synthase (DHPS) enzyme, while pyrimethamine takes down dihydrofolate reductase (DHFR)—both crucial for folate production in malaria parasites (Heinberg and Kirkman 2015). This combo also disrupts red blood cells and tissues, with sulfadoxine dragging out the drug's effects. But the game changes with mutations in the dhps and dhfr genes, which mess with the drug-binding ability of DHFR and seriously undermine sulfadoxine-pyrimethamine's effectiveness against *P. falciparum*. (Fitri *et al*., 2023).

pyrimethamine inhibits thymidylate synthase (TS), while sulfadoxine targets the 7, 8-dihydro-6-hydroxymethylpterin pyrophosphokinase (PPPK) enzyme. Both of these enzymes play crucial roles in the folic acid biosynthesis pathway. Research indicates that resistance to Sulfadoxine-Pyrimethamine (SP) is linked to specific point mutations in the DHFR-TS and PPK-DHPS genes (Yaro 2009).

Sulphadoxine-Pyrimethamine-resistance, has been noted in several regions across Africa. This resistance has compromised the effectiveness of intermittent preventive treatment for pregnant women and infants (Usoro *et al*., 2024). *Plasmodium* has developed resistance to antifolate drugs, especially the Sulfadoxine-Pyrimethamine (SP) combination. Antifolates target folate metabolism, which is crucial for the survival of malaria parasites. These drugs are powerful and work together to prevent and treat malaria. Despite their effectiveness, the malaria parasite has become resistant to antifolates. This resistance occurs through point mutations that affect two critical enzymes in the folate production pathway: dihydrofolate reductase and dihydropteroate synthase (Ananda *et al*., 2024).

The genetic foundations of antifolate resistance are likely the well-understood among various drug-resistance mechanisms. High-level resistance to pyrimethamine is caused by mutations in the DHFR gene, particularly at codons 108, 59, 51, and 164, leading to variations such as Ser108Asn, Cys59Arg, Asn51Ile, and Ile164Leu. Resistance to sulfadoxine in cultivated parasite lines is generally associated with mutations in the DHPS gene at codons 436, 437, 581, and 613 (Kumar and Mahato 2024).

Due to increasing chloroquine resistance, the antifolate drugs, specifically the sulfadoxine-pyrimethamine combination, are now used to treat *falciparum* malaria. These antifolate drugs mainly work by inhibiting DHFR and targeting the folate biosynthesis process in the malaria parasite, *P. falciparum* (Upadhyay 2016). Studying resistance to antifolate drugs has proven to be simpler compared to chloroquine resistance, largely because the main molecular targets of these drugs were identified through bacterial studies conducted in the 1930s and 1940s (Hyde 2009). The genetic basis of resistance to antifolate drugs resembles that of chloroquine resistance, with a few specific point mutations in the target genes being largely responsible for the resistance. In addition to traditional drug-binding and kinetic studies on recombinant enzymes, recent research involving parasite transfection where resistant DHFR and DHPS gene sequences are introduced into the genomes of sensitive parasites has directly demonstrated that the mutations found in field samples cause drug resistance in live parasites (Hyde, 2009). Similarly, common mutations in the DHPS gene that reduce the effectiveness of Sulfadoxine include codon changes such as A437G/K540E in Africa and A437G/A581G or A437G/K540E/A581G in Southeast Asia, with the latter pattern also seen in some parts of South America (Hyde 2002, Gregson and Plowe 2005). In Africa, where resistance to Pyrimethamine-Sulfadoxine is most significant, the most prevalent genotypes in highly resistant parasites combine triple mutations in DHFR with double mutations in DHPS. This specific pattern serves as a reliable marker for this type of resistance and is a strong predictor of the clinical outcome (Kublin *et al*., 2002). In Southeast Asia and South America, a fourth mutation, I164L, is commonly observed in DHFR. When combined with the other mutations, this alteration makes the parasites fully resistant to effective concentrations of Pyrimethamine-Sulfadoxine (Price *et al*., 2004). The spread of mutant parasites into Africa would be catastrophic, especially since many countries are currently relying on Sulfadoxine-Pyrimethamine as their primary treatment. The latest antifolate combination, chlorproguanil/dapsone (LapDap®), introduced in 2003, would also be compromised. Alarmingly, reports of these resistant parasites are already emerging from parts of East Africa (Sidhu *et al*., 2006).

4.3 Mechanisms of Resistance to Artemisinin

Artemisinin, derived from the Chinese herb *Artemisia annua*, is incredibly potent due to its reactive epoxide bridge, which is crucial for its antiparasitic effect. Sodium artesunate is the most powerful form, reducing parasite numbers by around 10,000-fold in just 48 hours. But using this drug alone, as first noticed in 1970s China, poses risks: recent studies show reduced effectiveness in parasites that reappear after seven days of artesunate monotherapy (Menard et al., 2005). Originally, artesunate was combined with mefloquine starting in 1994 in Southeast Asia, where it's still effective. Today, artemisinin derivatives are being tested with other antimalarials like Lumefantrine, Piperaquine, Amodiaquine, and Sulfadoxine-Pyrimethamine in various regions (known as artemisinin combination therapy, or ACT) to combat the small number of parasites that escape the quickly metabolized Artemisinin. However, some combinations are under scrutiny, especially if the partner drug is already compromised (Duffy and Mutabingwa, 2006). In Africa, the use of Artemisinin derivatives combined with Amodiaquine or Lumefantrine has become standard (Halima *et al*., 2006). Compared to other antimalarial drugs, ART derivatives are incredibly effective at quickly eliminating parasitemia (Lin and Zaw 2015). Artemisinin resistance poses a severe threat to global public health, with the potential for

devastating impacts in sub-Saharan Africa due to its high malaria burden and poor monitoring and containment systems (Ambrose *et al*., 2012).

The WHO advises using Artemisinin-based Combination Therapies (ACTs) as the primary second-line treatment for uncomplicated *P. falciparum* malaria. The artemisinin component aims to cut down the number of parasites during the first three days of treatment, effectively reducing parasite biomass (World Health Organization, 2018). Due to the resistance of *P. falciparum* to commonly used antimalarial drugs like chloroquine (CQ) and sulfadoxine-pyrimethamine (SP), malaria-related mortality and morbidity have risen. In 2005, the WHO recommended ACTs as the first-line treatment for *P. falciparum* malaria in all malaria-endemic regions.

Researchers have found that artemisinins are highly effective across different stages of the Plasmodium life cycle, targeting both the asexual blood stages and the sexual gametocyte stages. This broad-spectrum activity could help reduce disease transmission in areas with low transmission rates (Neill *et al*., 2010). Artemisinin acts on the malaria parasite's unique SERCA-type Ca2+ATPase, known as PfATP6. Resistance to artemisinin occurs when this enzyme is inhibited (Bhattacharjee and Shivaprakash, 2016). Originally emerging from the malaria-endemic countries, including those in Africa (Mishra *et al*., 2016). Resistance to artemisinin, characterized by delayed parasite clearance after treatment with artesunate monotherapy or artemisinin-based combination therapies, has been reported in western Thailand and west Cambodia. This situation mirrors the past rise in resistance to Sulfadoxine-Pyrimethamine and chloroquine. Globally, artemisinin-based combination therapies are used for treating *Plasmodium falciparum* malaria. But now, southeast Asia is seeing a surge in artemisinin resistance. This resistance is marked by reduced effectiveness during the ring stage of parasite development and slower parasite clearance after treatment. This problem is directly driving up failure rates for these combination therapies (Kyaw *et al*., 2015).

A genome-wide scan pinpointed the K13 gene on chromosome 13 of *Plasmodium falciparum* as a key player in artemisinin resistance (Zaw and Myo, 2015). Mutations in the Kelch13 (K13) propeller domain are linked to slower parasite clearance both in laboratory settings and in real-life cases. The C580Y mutation is the most common in the Greater Mekong Sub-region, but several other mutations in or near the K13 region, such as N458Y, Y493H, R539T, and I543T, are also tied to resistance (WHO, 2014; Daily, 2016). Additionally, a mutation at position 263 of the PfATP6 enzyme drastically impacts how well the enzyme responds to artemisinin (Nagasundaram *et al*., 2016). As our understanding of these mutations evolves, so will the definition of artemisinin resistance. Currently, artemisinin resistance is categorized into suspected resistance, characterized by delayed parasite clearance or high levels of K13 mutants, and confirmed resistance, which involves both delayed clearance and the presence of validated K13 mutations in the same patient (WHO, 2016).

Artemisinin resistance is a more complex beast than resistance to other antimalarials, where transporter or enzyme mutations are more straightforward. Unlike other antimalarial resistance mechanisms that usually involve genetic changes. Artemisinin resistance largely hinges on mutations in the propeller region of the Plasmodium falciparum Kelch 13 (PfK13) gene (Oboh *et al*., 2018). To maintain ACT effectiveness, alternatives are being explored, such as sequential double combination ACT, extended dosing schedules, and triple ACT regimens. Clinical trials for triple ACT are showing promising results, including in treating multidrug-resistant malaria (NCT03355664 and NCT02453308) (Krishna, 2019; White, 2019).

5.0 Conclusion and Recommendations

Genetic mutations on certain ADR genes at specific positions on the genes are one of the main causes of *Plasmodium falciparum's* resistance to almost all classes of antimalarial drugs currently in use. Other factors that greatly contribute to antimalarial resistance in Plasmodium falciparum include drug pressure, sub-standard and sub-curative doses. To stop the transmission of resistance genes in a population, it is best to avoid using antimalarial medications at substandard or sub-curative dosages and to routinely check genetic alterations.

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