International Journal of Endorsing
HEALTH SCIENCE RESEARCH

IJEHSR

Review Article

# Pharmacokinetics and Pharmacodynamics of ACTs: Optimizing Antimalarial Efficacy and Preventing Resistance.

**Syed Abdal Hussain Shah[1], Haris Riaz Khan[2], Noman Ahmed[1], Mahar Awais[1], Asra Hassan[1], Maryum Murtaza[1], Beena Gul[1], Aliya Khan[1], Muhammad Najeeb Ullah[1] & Danish Aizaz[3]**

[1]Department of Medical Lab Technology, Faculty of Biological and Biomedical Sciences, The University of Haripur, Khyber Pakhtunkhwa-Pakistan.
[2]IAHS, Wah Medical College (POF Hospital), Wah Cantt, Rawalpindi, Pakistan.
[3]Department of Biomedical Sciences, Pak-Austria Fachhochschule Institute of Applied Sciences and Technology, Khyber Pakhtunkhwa-Pakistan.

Doi: 10.29052/IJEHSR.v13.i2.2025.107-119
**Corresponding Author Email:** harisriazkhan3@gmail.com
**Received** 22/03/2025
**Accepted** 30/05/2025
**First Published** 01/06/2025



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## Abstract

**Background:** Artemisinin-based combination therapies (ACTs) are the cornerstone of treatment for Plasmodium falciparum malaria. This review aims to analyze the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of ACTs, with emphasis on absorption, metabolism, excretion, efficacy, and resistance dynamics, especially in vulnerable populations such as children and pregnant women.

**Methodology:** A narrative review approach was used. Relevant peer-reviewed literature published between January 1990 and April 2024 was identified through databases including PubMed, ScienceDirect, Scopus, and Google Scholar. Search terms included combinations of "artemisinin," "ACT," "pharmacokinetics," "pharmacodynamics," "antimalarial resistance," and related terms. Studies were included if they addressed ACT pharmacology or clinical outcomes in the context of malaria treatment.

**Results:** Artemisinin derivatives, including artesunate, artemether, and dihydroartemisinin, exhibit rapid parasite clearance due to short half-lives, but require combination with partner drugs such as lumefantrine or piperaquine for prolonged efficacy. Factors such as CYP450-mediated metabolism, drug bioavailability, genetic polymorphisms, and altered pharmacokinetics in special populations significantly influence treatment outcomes. Population PK/PD modeling and fixed-dose combinations help optimize dosing and minimize resistance. However, challenges persist in overcoming regional resistance patterns and ensuring accessibility in resource-limited settings.

**Conclusion:** Optimizing ACTs demands an integrative understanding of drug behavior, individualized dosing strategies, and continued pharmacological research. Sustained treatment efficacy and malaria control depend on personalized medicine, improved adherence, and strategic surveillance of emerging drug resistance.

## Keywords

Artemisinins, Antimalarials, Plasmodium Falciparum, Drug Resistance, Parasite, Pharmacokinetics.

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## Introduction

The term malaria originates from the Italian phrase "malaria," meaning "bad air," which reflects the historical belief that the disease was caused by unhealthy air in marshy regions. Today, malaria is recognized as a serious and widespread parasitic disease that remains endemic in tropical and subtropical regions worldwide. It is caused by protozoan parasites of the genus Plasmodium, which are transmitted to humans through the bite of infected Anopheles mosquitoes. Among the five Plasmodium species that infect humans (P. falciparum, P. vivax, P. malariae, P. ovale, and P. knowlesi), P. falciparum is the most lethal and is primarily responsible for severe forms of the disease[1].

According to the World Health Organization (WHO), an estimated 241 million malaria cases were reported in 2020. By 2022, this number had increased to approximately 249 million new cases, resulting in 608,000 deaths globally[2]. The disease claimed the lives of approximately 627,000 individuals globally, with incidence and mortality rates increasing notably after the onset of the COVID-19 pandemic[3]. The African region bears the highest burden, accounting for 94% of global cases and 95% of deaths. WHO further reported that five countries Pakistan, Ethiopia, Nigeria, Uganda, and Guinea were responsible for an additional 5 million malaria cases globally between 2021 and 2022. In Ethiopia, transmission peaks during the rainy season (July–September), with patterns influenced by altitude and rainfall variability, making the epidemiology cyclical yet unpredictable[4].

Control strategies for malaria focus on both prevention of transmission and reduction of disease burden. Vector control remains pivotal, particularly through the use of insecticide-treated bed nets (ITNs) and indoor residual spraying (IRS). Additionally, environmental management strategies such as eliminating stagnant water and improving sanitation significantly reduce mosquito breeding habitats[5].

Treatment of malaria depends on the Plasmodium species and the severity of infection. Artemisinin-based combination therapies (ACTs) are the standard of care for uncomplicated P. falciparum malaria, with dihydroartemisinin-piperaquine (DHA-PPQ) and artemether-lumefantrine (AL) being among the most widely used combinations. Chloroquine remains effective in regions without resistance for P. vivax and P. ovale, while primaquine is used to eliminate liver-stage hypnozoites and prevent relapse. Severe malaria is managed with intravenous (IV) or intramuscular (IM) artesunate followed by a complete ACT course, supported by adjunctive measures such as fluid therapy, antipyretics, and blood transfusions when necessary[6].

ACTs have been in use since the early 1990s. Their emergence was prompted by rising resistance in Southeast Asia to older therapies like mefloquine, sulfadoxine-pyrimethamine (SP), and chloroquine. In 1979, Chinese scientists elucidated the chemical structure of qinghaosu (artemisinin), a potent antimalarial compound derived from Artemisia annua (sweet wormwood). ACTs were swiftly adopted in Southeast Asia, with Vietnam beginning local production of DHA–piperaquine combinations as early as 1995[7].

Artemisinins are among the most effective antimalarial drugs available, capable of reducing the parasite biomass of P. falciparum by up to 10,000-fold during each 48-hour asexual life cycle. However, due to their short half-life (approximately one hour) and the potential for inducing parasite dormancy, artemisinins are unsuitable for monotherapy. As early as 1984, treatment failure (recrudescence) was observed in up to 40% of patients treated with high-dose artemisinin monotherapy, prompting the recommendation for combination therapies with longer-acting partner drugs. One of the earliest successful ACTs was the combination of artesunate and mefloquine, which showed high efficacy and good tolerability in Western Thailand for multidrug-resistant malaria[8].

The WHO currently recommends six ACTs based on regional drug efficacy and resistance patterns: DHA-piperaquine, artemether-lumefantrine, artesunate-amodiaquine, artesunate-mefloquine,

artesunate-sulfadoxine-pyrimethamine, and more recently, artesunate-pyronaridine[9, 10]. Nevertheless, there is growing concern about treatment failures even with intravenous artesunate in severe falciparum malaria[11]. Notably, in Eastern Cambodia and Southwestern Vietnam, increased rates of therapeutic failure have been associated with dihydroartemisinin-piperaquine, previously a frontline therapy[8].

This review aims to critically assess the pharmacokinetics and pharmacodynamics of ACTs, discuss the limitations of current regimens, investigate emerging resistance, and propose future therapeutic innovations. In ACTs, long-acting agents such as amodiaquine, mefloquine, sulfadoxine-pyrimethamine, and lumefantrine help clear residual parasites, while fast-acting agents such as artemisinin and its derivatives (e.g., artesunate, artemether, artemotil) rapidly reduce parasitemia[12]. The combination ensures rapid initial parasite clearance with prolonged post-treatment prophylaxis, thereby reducing the risk of resistance and recurrence[13].

Historically, artemisinin monotherapy (5-day regimen) was highly effective but plagued by relapse due to its short plasma half-life (1.4 to 2.6 hours)[14–16]. Pharmacokinetic studies in patients and healthy volunteers revealed that artemisinin concentrations declined by 70–80% between day one and day seven of dosing[17]. This decline is attributed to auto-induction of hepatic enzymes responsible for drug metabolism. Specifically, artemisinin is primarily metabolized by CYP2B6, with minor roles for CYP2A6 and CYP3A4[18].

Repeated oral administration of artemisinin significantly induces enzymes such as CYP2C19 and CYP2B6 doubling their activity within a week[19]. Additionally, CYP3A and CYP1A2 are upregulated upon repeated exposure. When combined with piperaquine, artemisinin demonstrates superior parasite and fever clearance, comparable in efficacy to DHA–piperaquine and artesunate–mefloquine, though artemisinin-piperaquine causes fewer gastrointestinal side effects[20, 21].

The pharmacokinetics of intravenously administered artemisinin remain inadequately studied. Its oral bioavailability is also limited due to poor gastrointestinal absorption and significant first-pass hepatic metabolism[17, 22]. Various approaches have been explored to improve its solubility and bioavailability, including complexation with β- and γ-cyclodextrins[23] and micronization to fine powder forms[24].

Artesunate (ART), a hemisuccinate ester of DHA and the most potent artemisinin derivative, is the treatment of choice for severe malaria. Intravenous ART is preferred for critical cases, while IM administration is recommended in peripheral facilities when IV access is not feasible prior to referral[24]. ART is also a key component of oral ACTs for uncomplicated malaria[25]. For non-severe cases, ART is effective at oral doses as low as 2 mg/kg, while tolerability has been demonstrated at maximum doses of up to 18 mg/kg, using intermittent (D1/D8) three-week cycles totaling 108 mg/kg[26].

## Methodology

### Eligibility Criteria

This review focused on peer-reviewed studies that provide relevant, empirical data on the pharmacokinetics, pharmacodynamics, efficacy, resistance, and dosing strategies of artemisinin-based combination therapies (ACTs) used in the treatment of malaria. Studies were included if they examined at least one ACT component or combination and presented findings related to Plasmodium falciparum. Only full-text articles published between January 1990 and April 2024 were considered. Reviews, meta-analyses, clinical trials, cohort studies, and pharmacological evaluations were included. Exclusion criteria comprised conference abstracts, editorials, commentaries, narrative reviews without original data, and case reports not directly addressing the pharmacological behavior of ACTs.

### Information Sources

The literature was gathered through a structured search across the following databases: PubMed, ScienceDirect, Scopus, and Google Scholar.

Additional manual screening of reference lists from key articles was also performed to identify relevant studies not captured in database searches.

**Search Strategy**

A comprehensive search strategy was developed using medical subject headings (MeSH) and free-text terms. The search terms included combinations of the following: "artemisinin," "artemisinin-based combination therapy," "ACT," "pharmacokinetics," "pharmacodynamics," "Plasmodium falciparum," "antimalarial resistance," "dose optimization," and "drug metabolism." Boolean operators AND and OR were used to maximize relevant search results. The search was limited to articles published in English between 1990 and April 2024.

**Selection Process**

After the initial search, 354 articles were retrieved. Two independent reviewers screened the titles and abstracts for relevance. Of these, 147 full-text articles were assessed for eligibility. Based on the defined inclusion and exclusion criteria, 63 high-quality and most relevant studies were ultimately selected and included in this review. Disagreements regarding study inclusion were resolved through discussion and consensus.

**Data Collection Process**

Data extraction was carried out using a standardized form developed to record key study characteristics. This included study design, population, ACT regimens, pharmacokinetic and pharmacodynamic parameters, dosing regimens, and resistance patterns. Each included study was read in full and the data synthesized manually to identify thematic trends.

**Data Items**

Key variables extracted from the studies included:

- Type of ACT (e.g., DHA-PPQ, AL, artesunate-mefloquine)
- Pharmacokinetic parameters (absorption, distribution, metabolism, elimination)
- Pharmacodynamic interactions (parasite clearance rate, recurrence)
- Resistance mechanisms (gene mutations, therapeutic failure)
- Dosing regimens (standard and alternative dosing strategies)
- Bioavailability challenges and solutions (e.g., micronization, co-formulation)
- Enzymatic involvement in drug metabolism (e.g., CYP2B6, CYP3A4, CYP2C19)

**Study Risk of Bias Assessment**

Although this review did not formally employ tools such as the Cochrane Risk of Bias tool, the quality of the included studies was assessed based on methodological rigor, clarity of pharmacokinetic/pharmacodynamic data, and relevance to clinical treatment of P. falciparum malaria. Preference was given to studies with clear definitions, reproducible methods, and statistically significant findings.

**Effect Measures**

For studies reporting therapeutic efficacy, measures such as parasite clearance time, recrudescence rate, treatment failure, and pharmacokinetic parameters like peak plasma concentration (Cmax), half-life (t1/2), and area under the curve (AUC) were noted. For comparative studies, odds ratios or relative risk values were extracted where available.

**Synthesis Methods**

The results from selected studies were synthesized qualitatively. Data were grouped thematically by ACT components and their pharmacological profiles. No meta-analysis was performed due to heterogeneity in study design, endpoints, and reporting metrics. Patterns and gaps in knowledge were identified, and areas requiring further research were highlighted.

**Reporting Bias Assessment**

The possibility of reporting bias was minimized by including multiple databases and conducting a broad search strategy. However, publication bias could not be entirely ruled out, especially for negative findings that may not have been published. Efforts were made to cross-reference

WHO reports and grey literature for balance and comprehensiveness.

## Pharmacokinetics of Artemisinin-Based Combination Therapies (ACTs)

The pharmacokinetic (PK) profiles of antimalarial drugs differ notably between malaria patients and healthy individuals. These characteristics also evolve as a patient's clinical condition improves. Moreover, significant PK variability exists within special populations such as pregnant women and children, necessitating population-specific dosing strategies[27].

### Absorption

Many antimalarial agents, particularly lipophilic and hydrophobic compounds, exhibit poor oral or intramuscular absorption, contributing to substantial interindividual variability in plasma concentrations. An inverse relationship is generally observed between bioavailability and fluctuation in blood concentration, highlighting the need to optimize drug formulations during the development phase[28].

Artemisinin and its derivatives (e.g., artemether, artesunate) demonstrate variable absorption profiles. Oral formulations are typically absorbed rapidly, achieving peak plasma concentrations within 1–2 hours[29]. However, food intake can influence this process, potentially delaying absorption and lowering peak levels. Artesunate, when administered intravenously, bypasses gastrointestinal absorption, resulting in immediate therapeutic plasma levels.

Traditionally, dosing strategies were based on average drug concentrations; however, patients at the extremes of exposure are at greater risk those with high concentrations are susceptible to adverse effects, while those with low levels are at risk of treatment failure and resistance development[30]. Therefore, comprehensive PK assessments that capture a wide range of drug levels across patient subgroups are essential. Due to the impracticality of frequent sampling in clinical settings, sparse sampling combined with population PK modeling is employed to optimize data collection and interpretation. This approach is particularly crucial in vulnerable groups such as pregnant women and children. If not undertaken during preregistration studies, these investigations should be prioritized in post-marketing phases[30].

### Distribution

During early drug development, PK variability particularly in distribution is not well understood. A core challenge is determining the extent of PK-PD data needed to support rational dose selection[31]. PK studies typically follow a stepwise approach: from preclinical models to healthy adults, followed by adult patients, children, neonates, and pregnant women.

Artemisinin compounds are highly lipophilic, allowing extensive distribution into body tissues. They predominantly bind to plasma proteins, especially albumin, which modulates their availability and therapeutic efficacy. Volume of distribution differs among derivatives; for instance, artemether exhibits a larger volume of distribution than artesunate, influencing its dosing schedule[32].

### Metabolism

Artemisinin derivatives, including artesunate, artemether, and dihydroartemisinin (DHA), undergo extensive hepatic metabolism mediated by the cytochrome P450 (CYP) enzyme system. Key metabolic enzymes include CYP3A4, CYP2B6, and CYP2C19, which generate active or inactive metabolites affecting overall bioavailability and clinical response[33].

Artesunate, a water-soluble prodrug, is rapidly hydrolyzed by plasma esterases into DHA, the most pharmacologically active metabolite. DHA is further metabolized via CYP3A4 and subsequently excreted in bile and urine. Artemether, being lipid-soluble, is also metabolized by CYP3A4 to form DHA, allowing for a longer half-life suitable for combination regimens. DHA itself undergoes glucuronidation by uridine diphosphate-glucuronosyltransferases (UGTs), facilitating

excretion. This process plays a central role in the detoxification of drugs and xenobiotics[15, 16].

Genetic polymorphisms in CYP enzymes lead to interindividual metabolic variability. For example, individuals with ultra-rapid CYP3A4 activity may clear drugs too quickly, risking treatment failure, while poor CYP2B6 metabolizers may experience drug accumulation and toxicity[34]. Drug-drug interactions further complicate this: CYP3A4 inducers (e.g., rifampicin, carbamazepine) accelerate metabolism and reduce drug exposure, while inhibitors (e.g., ketoconazole, grapefruit juice) may increase plasma levels and toxicity risk. Additionally, liver dysfunction can severely impair drug metabolism, necessitating dose adjustments[35].

These variations highlight the importance of personalized medicine. Fast metabolizers may benefit from more frequent or higher doses, while slow metabolizers may require dose reductions to avoid toxicity. Understanding these metabolic nuances is critical for optimizing ACT efficacy and safety[36]. For instance, in artemether-lumefantrine (Coartem), the longer half-life of lumefantrine complements the rapid DHA formation from artemether, ensuring sustained antiparasitic activity[37-39].

**Excretion**

Artemisinin and its derivatives are primarily excreted via hepatic metabolism and biliary-fecal elimination, with minimal renal clearance. Artesunate is rapidly converted to DHA, which is subsequently metabolized by CYP3A4 and UGTs, and mostly eliminated in feces; 20–30% of the drug is excreted in urine[40]. DHA itself is cleared rapidly, with a half-life of 1–3 hours, necessitating co-administration with longer-acting drugs. Artemether undergoes similar conversion and is eliminated mostly through the biliary system[41].

Partner drugs in ACTs have longer half-lives and are crucial for sustained parasite suppression. For example, lumefantrine (half-life: 3–6 days) is metabolized in the liver and excreted predominantly via feces (~80%) with minimal urinary excretion (~5%). Amodiaquine, used in the artesunate-amodiaquine (AS-AQ) combination, is converted in the liver to N-desethylamodiaquine, which has a prolonged half-life of 9–18 days and is mostly excreted in feces (70–80%)[42].

**Table 1: Summary of Elimination Pathways of Artemisinin-Based Combination Therapy.**

| Drug | Primary Metabolism | Primary Excretion | Half-life |
|---|---|---|---|
| **Artesunate → DHA** | CYP3A4 & UGTs (Liver) | Biliary (Feces) > Renal (Urine) | 30–60 min |
| **Artemether → DHA** | CYP3A4 (Liver) | Biliary (Feces) > Minimal Urinary | 2–3 hrs |
| **Dihydroartemisinin (DHA)** | UGTs (Liver) | Biliary (Feces) > Renal (Urine) | 1–3 hrs |
| **Lumefantrine** | CYP3A4 (Liver) | Biliary (~80%) > Renal (~5%) | 3–6 days |
| **Amodiaquine → N-desethylamodiaquine** | CYP enzymes (Liver) | Biliary (~70%) > Renal (~20%) | 9–18 days |

Due to minimal renal clearance, dose adjustments are generally not necessary for patients with renal impairment. However, hepatic dysfunction may require careful monitoring and potential dose modifications to avoid toxicity[6, 43].

The pharmacokinetics of artemisinin derivatives necessitate frequent dosing when used alone. Their rapid elimination renders monotherapy impractical for clinical use. Combining them with long-acting agents, as in ACTs, enables once- or twice-daily regimens, enhancing adherence and therapeutic success[41, 44].

## Pharmacodynamics of Artemisinin-Based Combinations

The pharmacodynamic (PD) activity of antimalarial drugs varies significantly depending on the developmental stage of the malaria parasite.

Among the various drug classes, 8-aminoquinolines show limited activity against the asexual stages of Plasmodium falciparum but are highly effective against pre-erythrocytic stages, hypnozoites (in P. vivax and P. ovale), and mature gametocytes[45].

In contrast, most other antimalarial drugs including ACTs are effective against the asexual and early sexual (gametocyte) stages of P. falciparum, P. vivax, P. malariae, P. ovale, and P. knowlesi. Notably, artemisinin derivatives such as artesunate, artemether, and DHA are unique in their ability to target both stage IV and early-stage V gametocytes of P. falciparum, thus possessing a broader spectrum of gametocytocidal activity[46].

Some antimalarials, like atovaquone and antifolates, have additional activity against the pre-erythrocytic stages and disrupt the mosquito life cycle (sporontocidal action) by inhibiting oocyst formation, helping prevent transmission. However, these drugs are not active against dormant liver-stage hypnozoites of P. vivax and P. ovale, with 8-aminoquinolines remaining the only effective class against these stages[45, 46].

**Mechanism of Action**

Artemisinin and its derivatives are among the most potent antimalarial agents known. Their primary mode of action is thought to involve the generation of reactive oxygen species (ROS), triggered by interaction with free iron derived from hemoglobin digestion by the parasite[47].

Once activated, the endoperoxide bridge in artemisinin reacts with heme iron, generating free radicals that inflict oxidative damage to vital parasite biomolecules proteins, lipids, and DNA leading to cell death.

This oxidative damage causes widespread dysfunction within the parasite, including membrane destabilization, mitochondrial damage, and misfolded proteins. These effects culminate in parasite death, typically within a single 48-hour asexual replication cycle[47, 48].

Recent evidence also suggests alternative or complementary mechanisms, such as the inhibition of parasite proteins and interaction with PfKelch13, a protein associated with artemisinin resistance, further contributing to its potent activity[48].

Due to its short half-life, artemisinin monotherapy is insufficient for complete parasite clearance. Therefore, Artemisinin-Based Combination Therapy (ACT) pairs artemisinin with a longer-acting antimalarial to ensure full parasite eradication and minimize the risk of resistance development[49]. This dual-action strategy is the foundation for ACT's exceptional efficacy in reducing parasite burden and halting resistance evolution[50].

**Efficacy, Safety, and Adverse Effects of ACTs**

The effectiveness of ACTs depends on achieving an optimal pharmacodynamic balance between sufficient drug exposure and therapeutic effect. Higher drug concentrations generally correlate with faster parasite clearance, but beyond a threshold, may not enhance efficacy and could instead elevate toxicity risks[51].

ACTs are generally well tolerated. Common mild side effects include gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Hypersensitivity reactions ranging from mild rashes to rare anaphylactic episodes can also occur. Neurological effects, though rare, may include headache, dizziness, or neuropsychiatric symptoms in some individuals[52].

To ensure safety, continuous pharmacovigilance and optimized dosing strategies are essential. The goal is to maximize treatment outcomes while minimizing adverse effects[51].

## Dosing Regimens for ACTs

Proper dosing is central to improving ACT effectiveness and reducing the emergence of resistance. Because ACTs rely on the synergy between a fast-acting artemisinin derivative and a long-acting partner drug, tailored regimens are essential for achieving therapeutic drug levels and ensuring parasite eradication[53].

**Weight- and Age-Based Dosing**

Dosing based on weight rather than age is preferred, especially in pediatric populations, as it ensures more precise drug exposure. Underdosing may lead to treatment failure and resistance, while overdosing can result in toxicity. Pediatric-friendly formulations, such as dispersible tablets, have been developed to facilitate accurate dosing in children[54].

**Fixed-Dose Combinations (FDCs)**

Fixed-dose combinations simplify regimens by co-formulating both drugs into a single tablet, improving treatment adherence and reducing the risk of incomplete dosing. FDCs such as artemether-lumefantrine or artesunate-amodiaquine are associated with better outcomes and lower rates of resistance development. Their synergistic pharmacologic action contributes to enhanced efficacy and tolerability[55].

**Dosing Modifications in Special Populations**

- Pregnant Women: Pregnancy alters drug pharmacokinetics due to increased blood volume, enhanced hepatic metabolism, and renal clearance, potentially reducing drug exposure[56]. For example, lumefantrine is metabolized more rapidly during pregnancy, leading to subtherapeutic levels. Some studies suggest extending treatment duration (e.g., 5 days) or adding extra doses to maintain efficacy, though more clinical data are needed to confirm safety[57, 58]. Artemether-lumefantrine is considered safe in the second and third trimesters, but not recommended in the first trimester, where quinine plus clindamycin is preferred[56].

- Children and Infants: Pediatric pharmacokinetics differ due to immature enzyme systems and altered body composition. Younger children, especially infants, may require adjusted dosing to avoid toxicity or subtherapeutic exposure[59].

For example, artemether-lumefantrine is dosed based on weight:

- 5 kg infant = 1 tablet/dose
- 15 kg child = 2 tablets/dose
- 25 kg child = 3 tablets/dose

This ensures proper exposure and minimizes risks [53, 59].

- Patients with Comorbidities: Liver and kidney dysfunction significantly impact drug metabolism and clearance. In hepatic disease, drugs like lumefantrine may accumulate, leading to side effects such as QT prolongation or neurotoxicity. In renal impairment, drugs like quinine require dose or interval adjustments to avoid accumulation[60]. Therefore, individualized dosing is crucial to balance efficacy and safety.

## Resistance and Challenges

**Dosing Strategies and Resistance Prevention**

As Plasmodium falciparum continues to evolve, resistance to ACTs poses a growing threat. Key strategies to delay or prevent resistance include:

- Ensuring complete adherence to prescribed doses and treatment duration. Partial treatment allows parasites to survive and develop resistance[61].
- Using long-acting partner drugs such as lumefantrine or amodiaquine to ensure any remaining parasites post-artemisinin clearance are eliminated[49].
- Prolonging treatment duration in regions with artemisinin resistance (e.g., from 3 to 5–7 days) to address delayed parasite clearance[62].
- Rotating ACT combinations or introducing new regimens with different partner drugs when resistance emerges, to maintain therapeutic effectiveness[63].

By carefully managing dosing regimens, exploring new drug combinations, and emphasizing patient adherence, we can preserve the efficacy of ACTs and ensure sustainable malaria control.

## Integration of Pharmacological Insights

### Synthesis of Pharmacological Insights

Artemisinin-based combination therapies (ACTs) demonstrate rapid parasite clearance and sustained efficacy by leveraging optimized pharmacokinetics. However, achieving optimal therapeutic outcomes requires personalized dosing strategies to account for metabolic variability, enhance bioavailability, and minimize the risk of resistance. Artemisinin derivatives such as artesunate, artemether, and dihydroartemisinin (DHA) are characterized by rapid absorption and short plasma half-lives (typically 30 minutes to 3 hours). Consequently, these agents must be co-administered with longer-acting partner drugs, including lumefantrine, piperaquine, and amodiaquine, which exhibit extended half-lives ranging from 3 to 18 days, ensuring sustained antimalarial activity and post-treatment prophylaxis.

The pharmacokinetic complementarity of artemisinin and its partner drugs underpins ACT efficacy, enabling immediate parasite burden reduction followed by prolonged suppression of residual parasites. However, metabolic variability particularly in hepatic metabolism mediated by cytochrome P450 enzymes (notably CYP3A4, CYP2B6, and CYP2C19) influences drug exposure. Repeated dosing of artemisinin derivatives induces auto-metabolism, decreasing drug plasma levels over time.

### Personalized Medicine and Population PK/PD Modeling

Genetic polymorphisms in these enzymes further affect drug clearance and efficacy: ultra-rapid metabolizers may eliminate the drug too quickly, reducing therapeutic benefit, while poor metabolizers may experience toxic accumulation. Absorption efficiency and formulation design also influence treatment success.

### Formulation Challenges and Optimization

Oral artemisinin formulations often suffer from low bioavailability due to poor solubility and high first-pass hepatic metabolism. Enhancements such as co-administration with food, formulation with cyclodextrin complexes, or other pharmaceutical modifications have demonstrated improved absorption profiles.

Special populations show altered pharmacokinetics. Pregnant women typically exhibit faster drug metabolism, resulting in lower plasma concentrations, whereas children may require weight-adjusted dosing due to immature hepatic enzyme systems and increased drug clearance.

Pharmacodynamic studies consistently affirm the potent efficacy of ACTs in rapidly reducing parasitemia. Artemisinin derivatives are especially effective against early asexual stages and immature gametocytes. The choice of partner drug, however, plays a critical role in determining the duration of post-treatment prophylaxis and resistance potential. Extended treatment durations and fixed-dose combinations (FDCs) enhance adherence and reduce the likelihood of resistance emergence.

Finally, population pharmacokinetic/pharmacodynamic (PK/PD) modeling has proven instrumental in optimizing dosing strategies particularly for vulnerable populations and in regions with emerging resistance patterns thereby improving therapeutic outcomes and programmatic planning.

## Implications and Interpretations

Artemisinin-based combination therapies (ACTs) have emerged as the global standard for treating uncomplicated Plasmodium falciparum malaria. The findings from this review underscore the central role of pharmacokinetic and pharmacodynamic optimization in maximizing the efficacy of ACTs, reducing resistance development, and ensuring safe and effective treatment regimens.

Artemisinin derivatives exert rapid antimalarial effects due to their fast action and short half-lives. However, their rapid elimination necessitates co-administration with partner drugs that sustain

antimalarial activity and provide post-treatment protection. Drugs like lumefantrine, piperaquine, and amodiaquine possess favorable half-lives that help prevent recrudescence and limit transmission. However, subtherapeutic exposure due to poor absorption, patient non-adherence, or host metabolic variability can facilitate the emergence of resistance, particularly in high-transmission settings.

One of the growing concerns is the geographical spread of artemisinin resistance, especially in Southeast Asia and parts of Sub-Saharan Africa. This resistance often arises when drug concentrations fall below therapeutic thresholds, allowing parasites to survive and propagate resistant phenotypes. These findings highlight the critical need for maintaining adequate drug levels throughout the full duration of treatment.

The review also draws attention to host-related factors, such as age, immune status, and pregnancy, which significantly influence drug pharmacokinetics. In particular, pregnant women and pediatric patients exhibit altered drug metabolism, requiring individualized dosing strategies. Additionally, drug-drug interactions and genetic polymorphisms affecting hepatic enzymes (e.g., CYP3A4) further complicate the achievement of therapeutic drug levels.

While tools like therapeutic drug monitoring and population PK/PD modeling have the potential to fine-tune dosing regimens, these strategies remain inaccessible in many resource-limited settings where malaria burden is highest. Consequently, there is an urgent need for simplified, evidence-based dosing algorithms that can be effectively implemented in the field without compromising efficacy or safety.

Ultimately, preserving the efficacy of ACTs will depend on an integrated approach one that combines robust pharmacological research, active resistance surveillance, rational drug policy, and regional customization of treatment protocols. The development of new partner drugs, next-generation ACTs, and strategies to delay resistance will be essential to sustaining global malaria control efforts.

## Conclusion

Artemisinin-based combination therapies (ACTs) remain the cornerstone of treatment for uncomplicated Plasmodium falciparum malaria, owing to their unmatched speed of action and high cure rates. Their therapeutic success lies in the synergistic pharmacological properties of fast-acting artemisinin derivatives and longer-acting partner drugs, which together enable rapid parasite clearance and sustained post-treatment protection. A comprehensive understanding of the absorption, distribution, metabolism, and elimination (ADME) profiles of each component drug is critical for optimizing dosing strategies. Particular attention must be paid to inter-individual variability in drug metabolism, primarily influenced by hepatic enzyme activity (e.g., CYP3A4) and genetic polymorphisms. These differences are especially relevant in special populations such as children, pregnant women, and patients with liver or kidney impairment, where inappropriate dosing may lead to treatment failure or toxicity. Ensuring patient adherence, correct dosing, and therapeutic drug exposure is essential to preventing resistance and maintaining ACT efficacy. Continued success will require sustained investment in pharmacological research, development of new antimalarial agents, routine surveillance for resistance, and context-specific treatment guidelines. Integrating PK/PD insights into clinical practice and public health policy will be fundamental to advancing malaria control and working toward global eradication goals.

## Conflicts of Interest

The author(s) have no conflicts of interest.

## Acknowledgement

We would like to express our heartfelt gratitude to Dr. Aamer Ali Khattak (Late), Mr. Usman Ayub Awan, and Mr. Anas Saeed for their continuous encouragement, expert guidance, and insightful support throughout the development of this manuscript. Their valuable input and constructive

feedback contributed significantly to the quality and completion of this research. We are sincerely thankful for their contributions, which greatly enhanced the scientific value and clarity of our work.

## Funding

None.

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