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Artemisinin-Based Combination Therapies vs Monotherapy: Resistance Prevention in Plasmodium falciparum Malaria

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ABSTRACT

Artemisinin resistance in Plasmodium falciparum posed a critical threat to global malaria control, with delayed parasite clearance and treatment failures increasingly reported across endemic regions. This review evaluated the biochemical rationale and clinical evidence supporting artemisinin-based combination therapies (ACTs) over monotherapy for preventing resistance emergence. A systematic literature review was conducted using PubMed, Cochrane Library, and WHO databases from 2015-2025, focusing on clinical trials, molecular surveillance studies, and mechanistic research. ACTs demonstrated superior efficacy in preventing resistance through complementary pharmacokinetic profiles that reduced selection pressure on artemisinin derivatives. PfKelch13 mutations remained the primary molecular marker for artemisinin resistance, with C580Y and other validated mutations showing strong correlation with delayed clearance phenotypes. Clinical evidence from Southeast Asia and sub-Saharan Africa confirmed that ACT deployment significantly reduced treatment failure rates compared to artemisinin monotherapy, with combination therapy providing protection factors ranging from 10-100 fold against resistance selection. Molecular surveillance demonstrated that regions with high ACT coverage maintain lower frequencies of kelch13 mutations. ACTs represented the most effective strategy for preserving artemisinin efficacy, though emerging partner drug resistance and suboptimal implementation threaten long-term sustainability. Enhanced surveillance, improved diagnostics, and next-generation combination regimens are essential for maintaining therapeutic effectiveness.

Keywords: Artemisinin resistance, Plasmodium falciparum, PfKelch13, Malaria treatment, Drug resistance surveillance.

INTRODUCTION

Malaria remains a leading cause of morbidity and mortality globally, with Plasmodium falciparum accounting for the most severe disease manifestations and deaths [1]. The introduction of artemisinin derivatives revolutionized malaria treatment through their rapid parasite clearance and broad-stage activity against asexual blood-stage parasites [2]. However, the emergence and spread of artemisinin resistance, first documented in western Cambodia in the early 2000s, represents one of the most significant threats to contemporary malaria control efforts [3]. Artemisinin resistance manifests clinically as delayed parasite clearance, with parasites surviving initial drug exposure through a dormancy mechanism that allows subsequent recrudescence [4]. The World Health Organization's recommendation for artemisinin-based combination therapies (ACTs) as first-line treatment was predicated on the pharmacological principle that combining artemisinin derivatives with partner drugs possessing different mechanisms of action would reduce selection pressure and prevent resistance emergence [5]. Extensive molecular epidemiological studies have identified mutations in the PfKelch13 gene as the primary determinant of artemisinin resistance, with specific mutations showing strong geographical clustering and association with delayed clearance phenotypes [6]. The objective of this review is to evaluate the biochemical mechanisms underlying artemisinin resistance, assess the clinical evidence supporting ACTs over monotherapy for resistance prevention, and examine current surveillance strategies and future directions for preserving antimalarial efficacy.

Molecular Mechanisms of Action and Pharmacology

Artemisinin derivatives exert their antimalarial activity through a unique mechanism involving iron-catalyzed activation within the parasite [7]. The endoperoxide bridge, a critical pharmacophore present in all artemisinin

compounds, undergoes cleavage in the presence of reduced iron (Fe^{2+}) or heme, generating highly reactive carbon-centered radicals [8]. This activation process occurs preferentially within parasitized erythrocytes due to the abundance of hemoglobin-derived heme from parasite digestion of host hemoglobin. The generated artemisinin radicals demonstrate broad reactivity, alkylating numerous parasite proteins and disrupting essential cellular processes [9].

Primary cellular targets of activated artemisinin include the parasite's food vacuole, where hemoglobin digestion occurs, and various metabolic enzymes critical for parasite survival. Key molecular targets identified through chemical proteomics approaches include PfATP6 (SERCA-type calcium pump), aldolase, and various proteins involved in parasite protein folding and stress response pathways [9]. The broad spectrum of protein targets explains artemisinin's rapid action against multiple parasite life cycle stages and its historically low propensity for resistance development.

The pharmacokinetic properties of artemisinin derivatives significantly influence their therapeutic efficacy and resistance selection potential [10]. Artemisinin compounds demonstrate rapid absorption, extensive distribution, and relatively short elimination half-lives (1-3 hours for most derivatives). This pharmacokinetic profile results in high peak concentrations that rapidly decline below minimum inhibitory concentrations, creating a selective pressure window during which partially resistant parasites may survive. Artesunate, the most widely used intravenous formulation, undergoes rapid hydrolysis to the active metabolite dihydroartemisinin, which demonstrates superior antimalarial potency compared to the parent compound [10].

Partner drugs in ACT formulations demonstrate contrasting pharmacokinetic profiles with longer elimination half-lives ranging from 1-6 days, depending on the specific compound [11]. Lumefantrine, piperaquine, mefloquine, and amodiaquine each possess distinct mechanisms of action targeting different parasite metabolic pathways. Lumefantrine and mefloquine disrupt parasite membrane function and hemoglobin digestion, while piperaquine and amodiaquine inhibit heme polymerization within the food vacuole. The extended presence of partner drugs provides sustained antimalarial activity after artemisinin derivatives have been eliminated, theoretically preventing survival of artemisinin-tolerant parasites.

The differential pharmacokinetic profiles create distinct selection pressure dynamics. Mathematical modeling studies demonstrate that the rapid decline of artemisinin concentrations, combined with the sustained presence of partner drugs, should minimize selection for resistance to either component [12]. However, this theoretical advantage requires optimal dosing regimens, adequate drug quality, and complete treatment adherence to maintain therapeutic concentrations throughout the treatment course.

Mechanisms and Molecular Basis of Resistance

The molecular basis of artemisinin resistance centers primarily on mutations in the PfKelch13 gene, located on chromosome 13 of P. falciparum [6]. Kelch13 encodes a propeller domain-containing protein involved in protein trafficking and potentially in the parasite's response to oxidative stress [13]. Validated artemisinin resistance-conferring mutations include C580Y, R539T, I543T, Y493H, and several others, predominantly clustered within the propeller domain region [14]. These mutations demonstrate strong geographical distribution patterns, with C580Y predominating in Southeast Asia and specific mutations emerging in different endemic regions [15].

The functional consequences of kelch13 mutations appear to involve enhanced parasite survival mechanisms during the early ring stage, when artemisinin susceptibility is typically highest [16]. Mutant parasites demonstrate increased dormancy capacity, entering a state of reduced metabolic activity that allows survival during periods of drug exposure [4]. This dormancy mechanism differs from classical drug resistance, as mutant parasites remain phenotypically sensitive to artemisinin in standard in vitro assays but demonstrate delayed clearance in clinical infections.

Beyond kelch13, additional genetic factors contribute to artemisinin resistance phenotypes. Copy number variations in genes encoding multidrug resistance proteins, including pfmdr1 and pfcrt, modulate artemisinin susceptibility and influence partner drug effectiveness [17]. Mutations in plasmepsin II/III genes affect piperaquine resistance, while pfcrt mutations influence chloroquine and amodiaquine activity [18]. These secondary genetic changes often emerge following initial kelch13 mutations, suggesting stepwise evolution toward multidrug resistance.

Biochemical models propose that kelch13 mutations alter the parasite's protein quality control systems, enhancing tolerance to artemisinin-induced protein damage [13]. Alternative hypotheses suggest altered heme handling or modified endoperoxide activation pathways. Recent proteomic studies indicate that kelch13-mutant parasites demonstrate enhanced antioxidant responses and modified protein trafficking patterns, supporting the oxidative stress tolerance model [19].

Laboratory assessments of artemisinin resistance employ multiple complementary approaches. The ring-stage survival assay (RSA) measures parasite survival after early ring-stage exposure to pharmacologically relevant artemisinin concentrations, providing a direct assessment of the dormancy phenotype [16]. In vitro susceptibility testing using standard 72-hour assays often fails to detect artemisinin resistance, highlighting the unique temporal

dynamics of resistance expression. Ex vivo assessments using fresh patient isolates provide additional phenotypic validation of genetically-determined resistance profiles.

Clinical resistance manifests as delayed parasite clearance following artemisinin treatment, typically defined as persistence of parasitemia 72 hours post-treatment initiation [20]. The parasite clearance half-life serves as a quantitative measure of artemisinin effectiveness, with values exceeding 5 hours indicating potential resistance [20]. However, host factors including immunity, parasite biomass, and concomitant infections influence clearance dynamics, complicating resistance assessment in field settings.

Rationale for Combination Therapy and Comparative Clinical Outcomes

The pharmacodynamic rationale for ACTs rests on the principle of combination chemotherapy, where drugs with independent modes of action and non-overlapping resistance mechanisms provide mutual protection against resistance selection [5]. The rapid, potent activity of artemisinin derivatives reduces parasite biomass by several logs within the initial 24-48 hours of treatment, while longer-acting partner drugs eliminate residual parasites and prevent recrudescence. This sequential action theoretically prevents selection of parasites resistant to either drug component.

Mathematical models demonstrate that monotherapy with artemisinin derivatives creates optimal conditions for resistance selection during the declining concentration phase, when drug levels fall below fully lethal concentrations but remain sufficient to select for resistant variants [12]. The addition of partner drugs with independent mechanisms extends the lethal concentration window, reducing the probability of resistance emergence by factors of 10-100, depending on the specific drug combination and parasite population characteristics.

Clinical evidence strongly supports ACT superiority over artemisinin monotherapy for both treatment efficacy and resistance prevention. Subsequent controlled trials in uncomplicated malaria consistently showed ACT cure rates exceeding 95% compared to 60-85% for artemisinin monotherapy, with significantly lower rates of late treatment failure [21].

Population-level evidence from Southeast Asia provides compelling support for ACT effectiveness in limiting resistance spread. Following WHO recommendations for ACT deployment in the early 2000s, regions with high ACT coverage demonstrated stabilization or reduction in kelch13 mutation frequencies, while areas with continued artemisinin monotherapy use showed progressive resistance increases [15]. The Tracking Resistance to Artemisinin Collaboration (TRAC) studies documented clear associations between ACT deployment and reduced resistance selection pressure across multiple endemic countries [22].

Large-scale effectiveness studies from sub-Saharan Africa demonstrate sustained ACT efficacy despite increasing resistance markers [23]. The World Antimalarial Resistance Network meta-analysis of over 50,000 patients treated with ACTs showed cure rates maintaining above 95% in most regions, with treatment failures primarily attributed to inadequate dosing, poor adherence, or partner drug resistance rather than artemisinin resistance per se [24].

However, ACT effectiveness faces significant challenges that may compromise resistance prevention. Substandard and falsified antimalarial drugs remain widespread, with studies indicating variable prevalence across markets, including regions where quality-assured ACTs represent only a minority of available products [25]. Poor quality drugs create subtherapeutic exposures that facilitate resistance selection. Additionally, incorrect dosing practices, particularly under-dosing in pediatric populations or patients with high body weight, reduce treatment efficacy and may promote resistance.

Partner drug resistance represents an emerging threat to ACT sustainability. Piperaquine resistance, associated with plasmepsin II/III copy number amplification and specific pfcrt mutations, has emerged across Southeast Asia, leading to high failure rates for dihydroartemisinin-piperaquine [18]. Similarly, lumefantrine tolerance associated with pfmdr1 amplification threatens artemether-lumefantrine effectiveness in some regions [17]. The emergence of partner drug resistance effectively converts ACTs to artemisinin monotherapy, recreating conditions favorable for artemisinin resistance selection.

Surveillance, Diagnostics, and Public Health Implementation

Comprehensive surveillance systems combining molecular, phenotypic, and clinical monitoring approaches are essential for tracking artemisinin resistance and informing treatment policy decisions [26]. Molecular surveillance focuses primarily on kelch13 genotyping, using PCR-based assays to detect validated resistance mutations in clinical isolates. WHO has established standardized protocols for kelch13 surveillance, with recommended thresholds for policy action when mutation frequencies exceed 5% in specific geographical areas [27].

Advanced molecular surveillance incorporates whole-genome sequencing approaches to detect novel resistance mutations and monitor genetic backgrounds associated with resistance [28]. Copy number variation assays for genes including pfmdr1, pfcrt, and plasmepsin genes provide additional insights into multidrug resistance patterns. These comprehensive genetic profiling approaches enable prediction of treatment outcomes and guide selection of appropriate ACT regimens.

Phenotypic surveillance employs standardized assays including the ring-stage survival assay and ex vivo susceptibility testing to validate molecular resistance markers and detect resistance phenotypes not captured by

current genetic markers [16]. The WHO Global Malaria Programme has established networks of reference laboratories capable of performing these specialized assays, though capacity remains limited in many endemic regions.

Therapeutic efficacy studies represent the gold standard for assessing clinical treatment effectiveness and detecting early signs of resistance emergence [27]. WHO protocols for conducting therapeutic efficacy studies provide standardized methodologies for measuring treatment outcomes, with recommendations for molecular resistance marker testing in treatment failures. These studies inform national treatment policy decisions and guide ACT selection for specific regions.

Quality assurance systems for antimalarial drugs play crucial roles in resistance prevention by ensuring therapeutic drug exposures [25]. Post-market surveillance using techniques including thin-layer chromatography and high-performance liquid chromatography identifies substandard products that may contribute to resistance selection. Patient adherence monitoring through directly observed therapy programs and pill counting methods helps ensure optimal drug exposure patterns.

Regional examples illustrate both successful resistance containment and failures in control efforts. The Greater Mekong Subregion's containment efforts, coordinated through WHO and partner organizations, successfully eliminated artemisinin-resistant P. falciparum from several border areas through intensive surveillance, vector control, and case management [29]. However, resistance continued to spread in areas with inadequate health system capacity and cross-border population movements.

In contrast, sub-Saharan Africa's experience demonstrates the challenges of implementing comprehensive surveillance in resource-limited settings [30]. While molecular surveillance has detected emerging kelch13 mutations in several countries, limited laboratory capacity and inadequate healthcare infrastructure complicate resistance monitoring efforts. The recent emergence of artemisinin resistance markers in Rwanda and Uganda highlights the need for strengthened surveillance systems across the continent [31].

Point-of-care diagnostic tools for resistance detection remain under development, though several promising technologies are advancing through validation studies. Rapid diagnostic tests capable of detecting kelch13 mutations could revolutionize resistance surveillance by enabling real-time treatment decisions in clinical settings. However, current technologies require further development to achieve the sensitivity and specificity required for clinical implementation.

Future Directions, Drug Development, and Policy Implications

Next-generation antimalarial drug development focuses on multiple strategies to overcome emerging resistance and extend the useful life of artemisinin derivatives [32]. Triple combination therapies, incorporating three drugs with independent mechanisms of action, represent the most promising near-term approach. The DHA-piperaquine-mefloquine combination demonstrated superior efficacy compared to standard ACTs in areas with emerging piperaquine resistance, though tolerability concerns limit widespread implementation [33].

Novel chemical entities targeting previously unexploited parasite pathways offer long-term solutions for artemisinin resistance [32]. Compounds including KAF156 (ganaplacide), KAE609 (cipargamin), and DSM265 target distinct parasite metabolic processes and demonstrate activity against artemisinin-resistant strains. Early clinical trials suggest these compounds may be suitable for combination with existing drugs or as components of next-generation combination regimens.

Drug repurposing efforts have identified existing compounds with antimalarial activity that could supplement current treatment options. Methylene blue, fosmidomycin, and certain antibiotics demonstrate antimalarial efficacy and may provide temporary solutions while novel drugs advance through development pipelines. However, most repurposed compounds require combination therapy to achieve adequate efficacy.

Resistance prevention strategies extend beyond drug development to encompass improved treatment guidelines, enhanced surveillance systems, and coordinated global responses [27]. The WHO Global Plan for Artemisinin Resistance Containment emphasizes early detection, rapid response, and sustained commitment to combination therapy principles. Implementation of this plan requires substantial investment in health system strengthening, particularly in sub-Saharan Africa where the greatest malaria burden persists.

Precision medicine approaches, utilizing rapid diagnostic testing for resistance markers, could enable tailored treatment selection based on local resistance patterns. This strategy requires development of reliable point-of-care resistance detection tools and establishment of treatment algorithms linking genetic markers to treatment recommendations. Early modeling studies suggest such approaches could significantly extend ACT useful life while maintaining treatment effectiveness [34].

Research gaps requiring urgent attention include improved understanding of artemisinin activation mechanisms, identification of novel resistance pathways beyond kelch13, and development of biomarkers predicting treatment failure. Enhanced pharmacokinetic-pharmacodynamic modeling incorporating resistance mechanisms could optimize dosing regimens for current ACTs and guide development of improved combination strategies.

Implementation research priorities include strategies for improving treatment adherence, ensuring drug quality in resource-limited settings, and developing sustainable financing mechanisms for next-generation antimalarials. Community engagement approaches and health system strengthening initiatives represent essential components of comprehensive resistance prevention strategies.

CONCLUSION

Artemisinin-based combination therapies represent the most effective strategy currently available for preventing artemisinin resistance in P. falciparum malaria, with compelling biochemical rationale and extensive clinical evidence supporting their superiority over monotherapy. The molecular mechanisms underlying artemisinin action and resistance provide clear pharmacological justification for combination approaches, while clinical trials and population-level studies consistently demonstrate reduced treatment failure rates and slower resistance emergence with ACT deployment. However, the effectiveness of this strategy depends critically on implementation quality, including drug quality assurance, appropriate dosing, treatment adherence, and comprehensive surveillance systems. The emergence of partner drug resistance and the continued spread of kelch13 mutations in some regions highlight the limitations of current ACT formulations and the urgent need for next-generation treatment strategies. Enhanced surveillance combining molecular, phenotypic, and clinical monitoring approaches is essential for early detection of resistance threats and informed policy responses. The development of novel antimalarial compounds and improved combination regimens offers hope for sustained malaria treatment effectiveness, though these solutions require substantial investment and coordinated global commitment. Key limitations of this review include the evolving nature of resistance surveillance data, geographical variations in resistance patterns that may limit generalizability of findings, and the inherent challenges of assessing long-term resistance prevention strategies in dynamic epidemiological contexts. Additionally, the complex interactions between host immunity, parasite genetics, and drug pharmacology require continued investigation to optimize treatment strategies for diverse endemic settings. National malaria control programs should maintain ACTs as first-line therapy while strengthening surveillance systems to monitor resistance emergence and implementing quality assurance measures to ensure optimal drug efficacy for resistance prevention.

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