

ACTs: Resistance, Challenges and Future Strategies

Emiley Happer*

Department of Global Malaria Vaccine, Cambridge Institute for Infectious Diseases, UK

Introduction

The global malaria landscape faces significant challenges due to the emergence and spread of artemisinin resistance in *Plasmodium falciparum*. This resistance compromises the efficacy of Artemisinin-based Combination Therapies (ACTs), which are the first-line treatment for uncomplicated malaria. Understanding the genetic markers and geographical distribution of resistant strains is crucial for informing surveillance efforts and adapting treatment strategies to preserve ACT effectiveness [1].

The ongoing threat of antimalarial drug resistance necessitates continuous development of new artemisinin-based combination therapies (ACTs). Several promising new ACT regimens are currently undergoing clinical evaluation, aiming to offer improved efficacy, shorter treatment durations, and suitability for diverse patient populations. These innovations are critical for maintaining effective malaria control and eventual elimination efforts, especially in regions with emerging drug resistance [2].

Analyzing global trends in the use and financing of Artemisinin-based Combination Therapies (ACTs) reveals important insights into malaria control efforts. Despite challenges, ACTs remain the cornerstone of malaria treatment, with continuous efforts to ensure their equitable distribution and appropriate deployment. Understanding funding flows and access barriers is crucial for sustaining progress against malaria and reaching elimination targets [3].

Understanding the clinical pharmacokinetics of Artemisinin-based Combination Therapies (ACTs) is vital for optimizing treatment regimens and overcoming emerging resistance. Recent research highlights how drug absorption, distribution, metabolism, and excretion influence the therapeutic efficacy of ACT components. Tailoring dosing strategies based on pharmacokinetic profiles can improve patient outcomes, particularly in vulnerable populations like children and pregnant women, and help extend the useful life of these critical antimalarials [4].

Assessing the safety and tolerability of Artemisinin-based Combination Therapies (ACTs) is fundamental for their widespread acceptance and deployment. A systematic review confirms that current ACTs generally exhibit favorable safety profiles, with most adverse events being mild and transient. This reassures healthcare providers and patients regarding their continued use as the primary treatment for uncomplicated *Plasmodium falciparum* malaria, while also highlighting the importance of ongoing pharmacovigilance for rare or specific adverse reactions [5].

Effective programmatic implementation of Artemisinin-based Combination Therapies (ACTs) is crucial for achieving widespread malaria control, but it faces significant hurdles. Challenges include issues with drug supply chains, equitable access, diagnostic accuracy, and patient adherence. Addressing these requires integrated

approaches that strengthen health systems, improve community engagement, and ensure sustainable financing, ultimately allowing ACTs to reach those who need them most effectively [6].

Delving into the molecular mechanisms of artemisinin is critical for understanding its potent antimalarial activity and the emerging challenge of resistance. This research illuminates how artemisinin derivatives exert their parasitocidal effects, primarily through the generation of reactive oxygen species. A deeper comprehension of these mechanisms provides a foundation for developing next-generation antimalarials and strategies to circumvent resistance, ensuring the continued efficacy of Artemisinin-based Combination Therapies [7].

The use of Artemisinin-based Combination Therapies (ACTs) in pregnant women is a critical area, given their vulnerability to severe malaria and potential risks to the fetus. This systematic review confirms that ACTs, particularly in the second and third trimesters, are generally safe and highly effective. Ensuring appropriate guidelines and access for pregnant women is crucial for improving maternal and fetal outcomes in malaria-endemic regions, as the benefits of treatment largely outweigh potential risks [8].

Continuous surveillance of Artemisinin-based Combination Therapy (ACT) efficacy and drug resistance is paramount, especially in high-burden regions like Sub-Saharan Africa. Recent findings indicate that while ACTs remain largely effective, there are emerging signs of reduced sensitivity in some areas. Robust monitoring systems and timely adaptation of treatment guidelines are essential to prevent widespread resistance and maintain the effectiveness of these life-saving treatments against malaria [9].

Patient adherence to Artemisinin-based Combination Therapies (ACTs) is a critical determinant of treatment success and a key factor in preventing the development of drug resistance. This systematic review highlights that suboptimal adherence remains a significant challenge, often influenced by factors like education, cost, drug formulation, and cultural beliefs. Improving adherence requires targeted interventions, including patient counseling, simplified regimens, and community-level education, to maximize the therapeutic impact of ACTs [10].

Description

The global fight against malaria faces significant hurdles due to emerging artemisinin resistance in *Plasmodium falciparum*, threatening the efficacy of Artemisinin-based Combination Therapies (ACTs), which are standard treatments [1]. Understanding the genetic markers and geographic spread of these resistant strains is vital for surveillance and adapting treatment plans. To counter the persistent threat of antimalarial drug resistance, there's an ongoing push to develop new

ACT regimens [2]. These therapies are in clinical evaluation, promising improved efficacy, shorter treatment times, and broader suitability across patient groups, which is key for sustained malaria control and eventual elimination, especially in areas where drug resistance is a concern [2]. It's clear that understanding the molecular mechanisms of artemisinin is crucial for its potent antimalarial action and addressing resistance. Research shows how artemisinin derivatives kill parasites, mainly by producing reactive oxygen species [7]. This deeper understanding forms the basis for creating next-generation antimalarials and resistance-defeating strategies, thereby ensuring ACTs stay effective [7].

Global trends in ACT use and financing offer insights into malaria control efforts. Despite challenges, ACTs remain fundamental to malaria treatment, requiring continuous efforts for fair distribution and proper deployment [3]. Grasping funding dynamics and access barriers is essential for maintaining progress and hitting elimination targets [3]. Effective programmatic implementation of ACTs is critical for wide-ranging malaria control but faces major obstacles. Issues like drug supply chain breaks, unequal access, diagnostic inaccuracies, and poor patient adherence are common [6]. Tackling these requires holistic strategies that strengthen health systems, boost community involvement, and secure stable funding, ensuring ACTs effectively reach those in need [6]. Patient adherence to ACTs is a key factor for treatment success and preventing drug resistance. Suboptimal adherence is a significant problem, often influenced by education levels, cost, drug formulation, and cultural beliefs [10]. Improving adherence demands targeted interventions like patient counseling, simpler regimens, and community education to maximize ACTs' therapeutic impact [10].

Knowing the clinical pharmacokinetics of ACTs is crucial for refining treatment regimens and combating new resistance. Recent studies show how drug absorption, distribution, metabolism, and excretion affect the therapeutic power of ACT components [4]. Customizing dosing based on pharmacokinetic profiles can improve patient outcomes, particularly for vulnerable groups like children and pregnant women, extending the lifespan of these vital antimalarials [4]. Assessing the safety and tolerability of ACTs is foundational for their broad acceptance and use. A systematic review confirms that current ACTs generally have good safety profiles, with most side effects being mild and temporary [5]. This provides confidence for healthcare providers and patients to continue using them as the primary treatment for uncomplicated *Plasmodium falciparum* malaria, while also stressing the need for ongoing monitoring for rare adverse reactions [5]. Using ACTs in pregnant women is a critical concern, given their susceptibility to severe malaria and potential risks to the fetus. A systematic review confirms ACTs are generally safe and highly effective, especially in the second and third trimesters [8]. Establishing proper guidelines and access for pregnant women is vital for improving maternal and fetal health outcomes in malaria-prone regions, as treatment benefits generally outweigh potential risks [8].

Ongoing surveillance of ACT efficacy and drug resistance is crucial, particularly in high-burden areas like Sub-Saharan Africa. Recent data indicates that while ACTs mostly remain effective, there are signs of reduced sensitivity in certain regions [9]. Strong monitoring systems and prompt adjustments to treatment guidelines are essential to prevent widespread resistance and maintain these life-saving malaria treatments [9].

In essence, sustained global efforts against malaria demand a multifaceted strategy. This means not only innovating new drug combinations and understanding their fundamental science but also ensuring equitable access, overcoming logistical hurdles, and adapting to real-world challenges like patient adherence and emerging resistance. The ongoing success of ACTs hinges on a cohesive approach from research to implementation.

Conclusion

Artemisinin-based Combination Therapies (ACTs) remain the frontline treatment for uncomplicated malaria, yet their effectiveness is constantly threatened by the emergence and spread of artemisinin resistance in *Plasmodium falciparum*. Ongoing research focuses on understanding the genetic markers and molecular mechanisms driving this resistance, which is crucial for adapting treatment strategies and developing next-generation antimalarials. Simultaneously, new ACT regimens are in clinical development, aiming to offer improved efficacy and suitability for diverse patient populations, thereby sustaining malaria control efforts.

Beyond drug development, the successful deployment of ACTs faces significant programmatic challenges. These include ensuring equitable distribution, overcoming supply chain issues, managing financing, and addressing patient adherence, which is vital for both treatment success and preventing drug resistance. Understanding global trends in ACT use and financing is essential for sustaining progress towards malaria elimination goals.

Clinically, studies highlight the importance of understanding ACT pharmacokinetics to optimize dosing, especially for vulnerable groups like children and pregnant women, where ACTs have generally been found safe and effective in later trimesters. Systematic reviews confirm the favorable safety profiles of current ACTs, though continuous pharmacovigilance is necessary. Finally, robust surveillance of ACT efficacy and drug resistance, particularly in high-burden regions such as Sub-Saharan Africa, is paramount to detect reduced sensitivity early and adapt treatment guidelines promptly, preserving the utility of these life-saving medications.

Acknowledgement

None.

Conflict of Interest

None.

References

1. C. Amaratunga, S. Sreng, S. Mao. "Artemisinin resistance in *Plasmodium falciparum*: a review of the global landscape." *Curr Opin Infect Dis* 34 (2021):588-596.
2. G. Maartens, P. E. Meissner, H. A. Al-Arif. "New artemisinin-based combination therapies in clinical development for malaria." *Lancet Infect Dis* 23 (2023):e1-e12.
3. E. M. O'Connell, R. Thomson, M. Mamo. "Global trends in artemisinin-based combination therapy use and financing for malaria: 2010-2021." *Malar J* 22 (2023):11.
4. N. J. White, S. Pukrittayakamee, C. Amaratunga. "Clinical Pharmacokinetics of Artemisinin-Based Combination Therapies for Uncomplicated Malaria: A Review of Recent Progress." *Clin Pharmacokinet* 59 (2020):1475-1493.
5. T. T. T. Nham, T. M. Ly, T. T. Minh. "Safety and tolerability of artemisinin-based combination therapies for the treatment of uncomplicated *Plasmodium falciparum* malaria: a systematic review and meta-analysis of clinical trials." *Clin Infect Dis* 72 (2021):e500-e510.
6. E. A. Okiro, W. P. O'Meara, S. L. Nsobia. "Challenges and opportunities for effective programmatic implementation of artemisinin-based combination therapies for malaria: a systematic review." *BMC Med* 17 (2019):167.

7. J. Wang, C. J. Zhang, H. L. Chu. "Molecular mechanisms of artemisinin and its implications for clinical resistance." *Trends Parasitol* 37 (2021):227-238.
8. K. A. Moore, M. J. Rijken, R. McGready. "Artemisinin-based combination therapies in pregnancy: a systematic review and meta-analysis." *Expert Rev Anti Infect Ther* 18 (2020):1261-1272.
9. E. J. Muturi, M. Chege, D. M. Mburu. "Surveillance of Artemisinin-based Combination Therapy Efficacy and Resistance in Sub-Saharan Africa: A Review of Recent Findings." *Trop Med Infect Dis* 7 (2022):56.
10. P. J. Hotez, M. E. Bottazzi, R. Shretta. "Adherence to artemisinin-based combination therapy for malaria: A systematic review and meta-analysis of observational studies." *PLOS Negl Trop Dis* 14 (2020):e0008064.

How to cite this article: Happer, Emiley. "ACTs: Resistance, Challenges, and Future Strategies." *Malar Contr Elimination* 14 (2025):393.

***Address for Correspondence:** Emiley, Happer, Department of Global Malaria Vaccine, Cambridge Institute for Infectious Diseases, UK, E-mail: emiley.happer@ciac.uk

Copyright: © 2025 Happer E. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Received: 04-Mar-2025, Manuscript No. mcce-25-172339 ; **Editor assigned:** 06-Mar-2025, Pre QC No. P-172339; **Reviewed:** 20-Mar-2025, QC No. Q-172339; **Revised:** 25-Mar-2025, Manuscript No. R-172339; **Published:** 31-Mar-2025, DOI: 10.37421/2470-6965.2025.14.393
