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ACTs: Safety, Efficacy and Effectiveness Challenges

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Introduction

Artemisinin-based combination therapies (ACTs) are central to malaria treatment globally, especially in sub-Saharan Africa. Extensive research explores ACT safety, efficacy, and factors impacting their success. This work is crucial for public health, guiding treatment guidelines, and ensuring these vital drugs remain effective. Studies often focus on vulnerable populations, like pregnant women and young children, and address challenges such as HIV co-infection and drug resistance.

The safety of ACTs, particularly in vulnerable groups, is a major research focus. One review summarizes safety data for ACTs in pregnant, lactating, and non-pregnant women across sub-Saharan Africa. It underscores the need for safe drugs, detailing existing evidence and identifying gaps in ACT safety profiles. While generally reinforcing ACT safety, it calls for more targeted research, especially for the first trimester of pregnancy and during breastfeeding, to create comprehensive safety guidelines [1].

A Ugandan prospective cohort study specifically investigated ACT safety during early pregnancy, a period often raising teratogenicity concerns. The findings offered crucial reassurance, noting no increased risk of adverse pregnancy outcomes, congenital anomalies, or fetal loss compared to non-exposed pregnancies. This evidence supports updated guidelines for broader ACT use in early pregnancy, aiming to save lives without fetal compromise [4].

Furthermore, a systematic review and meta-analysis confirmed ACT efficacy and safety for uncomplicated malaria in pregnant women in Africa. This research filled a critical knowledge gap, concluding ACTs are generally effective and safe, especially in the second and third trimesters. This supports their vital role in preventing maternal and fetal malaria-related morbidity and mortality [9]. Another systematic review assessed ACT safety in HIV co-infected individuals. It examined potential drug-drug interactions and adverse effects with antiretroviral drugs, which is crucial in high HIV prevalence regions. This review concluded that ACTs largely maintain a good safety profile in HIV-coinfected patients, but emphasized careful monitoring and further research on specific drug interactions for optimal co-treatment [2].

Beyond safety, ACT therapeutic efficacy remains fundamental to malaria control. Studies from diverse endemic settings consistently affirm their high effectiveness. For instance, Ugandan research assessed the in vivo efficacy of artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DHA-PQ) for uncomplicated Plasmodium falciparum malaria in children. This data, contributing to national and international guidelines, highlighted their sustained high efficacy, solidifying their role as first-line treatments while stressing the need for ongoing resistance surveillance [3]. Similarly, an Ethiopian multicentre trial confirmed the high efficacy and good safety profile of AL in children aged 6-59 months with uncomplicated falciparum malaria. These findings are vital for national control programs and global efforts [7]. In Ghana, a study on AL and DHA-PQ for uncomplicated Plasmodium falciparum malaria provided critical national drug policy data, confirming continued high efficacy. It also underlined the importance of constant monitoring for declining efficacy, a potential sign of emerging resistance [8]. Complementing these, in vitro susceptibility studies in Benin between 2018 and 2021 are essential for detecting early signs of drug resistance. Findings indicated sustained susceptibility, supporting current ACT efficacy but stressing the need for continuous surveillance to preempt resistance emergence [6].

The effectiveness of highly efficacious drugs like ACTs relies on proper usage and assured quality. A cross-sectional study from Eastern Uganda examined ACT adherence among children under five. It identified factors like caregiver knowledge, perceived drug efficacy, and healthcare access. Poor adherence can lead to treatment failure and drug resistance, highlighting the need for targeted health education and support to boost compliance and optimize ACT effectiveness in pediatric populations [5]. Equally crucial is drug quality. A study assessed ACT drug quality in Sierra Leone's health facilities and pharmacies. It found instances of substandard or falsified ACTs, a major public health concern. The study urged enhanced regulatory oversight, robust supply chain management, and continuous post-market surveillance to protect patients and preserve these essential antimalarial drugs' efficacy [10].

Description

Artemisinin-based combination therapies (ACTs) represent the frontline defense against Plasmodium falciparum malaria, especially in high-burden regions. However, maintaining their effectiveness is a complex endeavor, requiring continuous monitoring of safety, efficacy, and factors like patient adherence and drug quality. Understanding these aspects is vital for global health strategies and local implementation. The collective research underscores a multifaceted approach to malaria control, integrating clinical data with public health interventions. These studies often highlight regional specificities and global implications concerning malaria treatment. They contribute to a growing body of evidence supporting and refining current guidelines for ACT use across diverse populations.

A systematic review provided a broad synthesis of ACT safety during pregnancy, lactation, and in non-pregnant women in sub-Saharan Africa. While generally affirming ACT safety, it critically identified persistent knowledge gaps, particularly regarding first-trimester exposure and breastfeeding, emphasizing the need for targeted research to ensure truly comprehensive guidelines [1]. Complementing this, a prospective cohort study specifically in Uganda offered substantial reassurance for ACT use in early pregnancy. This study found no elevated risks for adverse pregnancy outcomes, congenital anomalies, or fetal loss, a crucial finding

that supports broader ACT utilization in early gestation to combat malaria without compromising fetal health [4]. Further validating these findings, another systematic review and meta-analysis focused on ACTs for uncomplicated malaria in pregnant African women. This work confirmed general efficacy and safety, especially in the second and third trimesters, which is key for reducing maternal and fetal morbidity and mortality from malaria [9]. Additionally, the safety of ACTs in HIV co-infected patients, a significant concern due to potential drug-drug interactions with antiretrovirals, was addressed by a systematic review. It concluded that ACTs largely maintain a good safety profile in this population but called for continued vigilance and specific research into interactions for optimized co-treatment strategies [2].

The efficacy of ACTs remains a central theme, with studies consistently showing high performance. In Uganda, the in vivo efficacy of artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DHA-PQ) in children with uncomplicated Plasmodium falciparum malaria was assessed. This research confirmed their sustained high efficacy, directly informing national and international treatment guidelines and stressing the need for ongoing surveillance for potential resistance [3]. Similarly, a multicentre clinical trial in Ethiopia investigated AL in young children (6-59 months) with uncomplicated falciparum malaria, reconfirming its high efficacy and strong safety profile. These results are instrumental for national malaria control programs and broader global efforts to protect pediatric populations [7]. In Ghana, therapeutic efficacy studies on AL and DHA-PQ between 2019-2020 further supported their continued high efficacy for uncomplicated Plasmodium falciparum malaria. The study reinforced their role as first-line treatments but also highlighted the crucial need for continuous monitoring to detect any decline in efficacy, which would be a red flag for emerging drug resistance [8]. This concern about resistance is further explored by in vitro susceptibility studies, such as one conducted in Benin from 2018 to 2021. This research evaluated Plasmodium falciparum susceptibility to artemisinin and its partner drugs. While demonstrating sustained susceptibility, it underscored that constant surveillance is absolutely necessary to preempt and contain the spread of resistance [6].

Beyond the inherent properties of ACTs, practical aspects like patient adherence and drug quality significantly impact treatment success. A cross-sectional study in Eastern Uganda focused on adherence to ACTs among children under five. It pinpointed factors such as caregiver knowledge, perceptions of drug efficacy, and access to health services as key influences. Crucially, the study warned that poor adherence could lead to treatment failure and drug resistance, advocating for targeted health education and support programs to enhance compliance and overall ACT effectiveness in these vulnerable pediatric groups [5]. In parallel, concerns about the quality of ACT drugs themselves are a serious public health issue. An assessment in Sierra Leone's health facilities and pharmacies uncovered instances of substandard or falsified ACTs. This finding prompted strong recommendations for improved regulatory oversight, more robust supply chain management, and diligent post-market surveillance. These measures are essential to safeguard patients and ensure the continued efficacy of these critical antimalarial treatments against the threat of widespread resistance [10].

In sum, the research collectively paints a picture of ACTs as highly effective and generally safe drugs, particularly for uncomplicated malaria in various populations, including pregnant women and children. However, the studies also consistently highlight that their long-term effectiveness hinges on vigilance: continuous surveillance for resistance, rigorous monitoring of drug quality, and concerted efforts to improve patient adherence. These findings reinforce the complexity of malaria control, demonstrating that scientific advancements in drug development must be accompanied by strong public health infrastructure and patient education to achieve lasting impact.

Conclusion

Artemisinin-based combination therapies (ACTs) are the cornerstone of malaria treatment, with extensive research focusing on their safety, efficacy, and factors influencing their effectiveness. Multiple studies confirm the general safety profile of ACTs. For instance, research synthesizes data on ACTs in pregnant, lactating, and non-pregnant women across sub-Saharan Africa, reinforcing their safety but pointing to gaps for first-trimester pregnancy and breastfeeding [1]. A prospective cohort study in Uganda further reassured the safety of ACTs during early pregnancy, finding no increased risk of adverse outcomes [4]. Similarly, ACTs generally maintain a good safety profile in HIV-coinfected patients, though drug interactions need careful monitoring [2].

Efficacy remains consistently high for key ACTs like artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DHA-PQ) in treating uncomplicated Plasmodium falciparum malaria in children in Uganda [3], Ethiopia [7], and Ghana [8]. This strong performance supports their continued use as first-line treatments. However, effective treatment also relies on adherence; poor compliance, as observed in Eastern Uganda among children under five, can lead to treatment failure and resistance [5]. Vigilant surveillance is also essential. In vitro susceptibility studies in Benin show sustained susceptibility, but highlight the need for constant monitoring to detect resistance early [6]. Finally, ensuring the quality of ACT drugs is paramount, with studies revealing issues of substandard or falsified ACTs in places like Sierra Leone, underscoring the need for stronger regulatory oversight [10]. Overall, ACTs are effective and safe for pregnant women, particularly in later trimesters [9], with calls for more specific first-trimester data.

Acknowledgement

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Conflict of Interest

None.

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