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Perspective

A Temporizing Solution to "Artemisinin Resistance"

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Antimalarial drug resistance has arisen frequently in the past, causing familiar treatment regimens to fail, with sometimes devastating consequences. Resistance has eventually been managed when new treatments have been developed, but drug discovery is a painstaking process that takes decades of effort and considerable investment.

Despite successes of malaria-eradication campaigns launched by the World Health Organization in the 1950s, the emergence of drug-resistant parasites in many malaria-endemic areas resulted in failures of response to inexpensive drugs such as chloroquine. These failures stimulated investments in drug-discovery programs, including a national project set up by the Chinese government to consolidate its research resources. The dedication of hundreds of scientists and decades-long efforts (as part of Project 523) led to our discovery of artemisinins.

Artemisinin derivatives, used in carefully developed combinations, have since served as the first-line drugs against most uncomplicated malaria infections. Artemisinins are combined with other drugs so that the fast-acting artemisinin can immediately reduce parasitemia, allowing remaining parasites to be removed by a long-acting partner drug. Monotherapy with the artemisinin compound artesunate is used for initial management of severe disease. In geographic areas where artemisinin combinations work, there is no need to modify treatments.

A slowdown in the clearance of parasites in patients treated with artesunate sounded alarms when it was first reported from Cambodia. Subsequently, similar delays in parasite clearance were noted in countries in Asian territories, including Myanmar, Thailand, Laos, and China, collectively referred to as the Greater Mekong Subregion.[1] It was determined that parasites that were cleared more slowly after artemisinin treatment carried mutations in the propeller domain of the malarial *kelch13* (*K13*) gene. Although *K13* mutations are not reliably associated with increased risk of treatment failure, parasites bearing these mutations are now called "artemisinin-resistant." Phenotypically, "artemisinin resistance" is defined as a delay in parasite clearance. These parasites recrudesce more frequently than artemisinin-sensitive parasites after standard 3-day therapeutic courses with artemisinin combination treatments (ACTs).

However, 3-day courses do not contain the full treatment doses of artemisinins needed to cure

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infections, which last 7 to 10 days, according clinical studies conducted in China. When a 7-day treatment course of artesunate is used, it is effective even when early parasite clearance is delayed.[2] The same is not true of resistance to other classes of antimalarials, which results in a failure to cure the infection after a full treatment course.

Should a delay in parasite clearance with artemisinin treatments be defined as drug "resistance" or "tolerance"? Either way, 3-day therapeutic courses are losing their efficacy against malarial parasites in the Greater Mekong Subregion. So what matters most to patients and populations at risk is how we handle this emerging threat.

We propose that the continued rational and strategic use of ACTs is the best, and possibly the only, solution to treatment failures for the foreseeable future. This proposition is based on two considerations related to artemisinins and their contribution to successful antimalarial therapies.

The first consideration is that current artemisinin resistance continues to manifest as delayed parasite clearance with no evidence of full resistance phenotypes. Artemisinins remain effective, even if they require a longer treatment course or other modifications to the combination-treatment regimen. By contrast, when parasites have developed resistance to other antimalarials, cure rates achieved with full treatment courses have fallen. Treatment failures with artemisinin combination therapy can be directly attributed to the partner drug, despite delayed-parasite-clearance phenotypes.[2] For example, if piperaquine–dihydroartemisinin treatment is failing in a given region, another combination, such as mefloquine plus artesunate, may prove very effective. This reciprocal relationship in sensitivities to different artemisinin-containing combinations (whereby parasites that are, for example, resistant to piperaquine tend to be sensitive to mefloquine and vice versa) is associated with resistance mechanisms (here, *pfmdr1* copy number) that influence the efficacy of the artemisinin partner drug and not of the artemisinin itself.[3]

Why is the partner drug failing and not the artemisinin component of the combination? Recent clarification of the mechanism of action of artemisinins reveals that they are prodrugs activated by iron or heme.[4] Iron and heme are by-products of hemoglobin digestion that reach their maximal concentrations in maturing trophozoite stages of malaria parasites. Once activated, artemisinins alkylate numerous parasite proteins and heme. Heme alkylation also inhibits the process of heme detoxification. This unique activation and widespread targeting mechanism suggests that mutations in individual protein targets are stochastically unlikely to cause resistance,[4] and it may explain why artemisinins remain efficacious after decades of widespread use.

Can the mechanism of action also explain the delayed-parasite-clearance phenotype? The elimination half-life of artemisinins in the blood is relatively short, whereas concentrations of free heme and iron fluctuate dramatically throughout the parasite life cycle and are low in early ring stages. Parasites stand a better chance of surviving if they stay in the early ring stage of development, when hemoglobin degradation is limited. Even artemisinin-sensitive malaria strains can appear resistant to artemisinin treatment when they are synchronized and exposed in the early ring stages of infection. Artemisinin-resistant strains (with the prolonged-clearance phenotype) have an altered life cycle that minimizes activation of artemisinins with a lengthened ring stage and a shortened trophozoite stage. They have also evolved stronger stress-response pathways that repair cellular damage resulting from limited artemisinin targeting in ring stages. These alterations better position the parasites to thrive after the effects of short-term exposure to artemisinins have waned. Crucially, when they reach the trophozoite stage, "artemisinin-sensitive" and "artemisinin-resistant" parasites respond equally well to artemisinins. Parasite "resistance" thus reflects the time for which parasites can outlast short exposures to artemisinins by minimizing their period of vulnerability.

This understanding clarifies how so-called artemisinin resistance can be managed. Because artemisinins are well tolerated, strategies that increase the drug exposure of parasites in their vulnerable trophozoite stage should be seriously considered. Relatively minor adjustments such as extended treatment durations effectively overcome the current "artemisinin-resistance" phenotype.[5] It remains entirely possible to rely on artemisinin and its partner drugs to eliminate malaria in the Greater Mekong Subregion by modifying the current standard regimens and accounting for partner-drug resistance. Interventions involving existing combinations (optimized to maintain high cure rates) should be taken soon after infections are diagnosed in regions and before any new complications emerge.

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The second consideration is whether we have any promising alternatives to artemisinins. There are praiseworthy and encouraging results from academic, public, and private partnerships such as the Medicines for Malaria Venture. But the unpredictability of the drug-development process should not be underestimated. Spiroindolones are potent antimalarials that were identified in chemical screening initiatives, but drug-resistance mutations in the malaria parasite cation ATPase PfATP4, their proposed target, have emerged even before they have been given to patients. Resistance risks can be reduced by combining new drugs with existing antimalarials. But the commonest (nonartemisinin) partner drugs are themselves prone to reduced efficacy.

A next-generation antimalarial that compares favorably with artemisinins in potency, safety, and risk of resistance seems unlikely to emerge soon. Most ACTs are inexpensive (less than $10, for example, for a treatment course of artemether–lumefantrine in Ghana). The high costs of drug-development programs affect the price of new products and may preclude access for the neediest patients.

Four decades after their development, artemisinins remain the antimalarial class of choice when used in combination therapy. Even as monotherapy, artesunate suppositories have reduced mortality by 96% when malaria has been treated in inaccessible Zambian villages, according to the Medicines for Malaria Venture. Thus, we see nothing to prevent simple adjustments to existing regimens, including intelligent use of combinations of drugs with reciprocal sensitivities, from maximizing the potential of our strongest weapon against malaria. We believe that it is urgent for these actions to be implemented.

Dr. Krishna is a member of the WHO Malaria Treatment Guidelines Group, which produces global guidance on the treatment of malaria, including decisions about artemisinin combination therapies. The views expressed in the article are those of the authors and do not necessarily represent those of the WHO.

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