Are three drugs for malaria better than two?

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Malaria, in particular that which is caused by *Plasmodium falciparum*, remains a huge problem, and its control is threatened by resistance to available drugs.[1] The most important antimalarial drugs available are artemisinin-based combination therapies (ACTs), which include a rapid-acting artemisinin component plus a slower-acting partner drug. The artemisinin rapidly kills parasites, but, with a standard 3-day regimen, might not eliminate all *Plasmodium*. The partner drug eliminates remaining parasites and restricts selection of artemisinin resistance.

Despite their pharmacologically mismatched components, ACTs offer remarkable efficacy for the treatment of uncomplicated malaria caused by drug-sensitive parasites. However, ACT resistance, which manifests as delayed clearance of parasites after initiation of therapy, and is mediated by mutations in a Kelch (K13) protein of *P falciparum*, is now widespread in parts of southeast Asia.[2,3] Furthermore, resistance to the ACT partner drugs mefloquine[4] and piperaquine[5] has moved artemisinin resistance from a mainly theoretical concern, since ACTs are still generally effective with resistance only to the artemisinin component, to a pressing problem. Treatment with the previous national regimen dihydroartemisinin-piperaquine, for example, is failing for most patients infected with *P falciparum* in parts of Cambodia.[6]

With artemisinins limited by their delayed clearance phenotype and partner drugs failing, our ability to treat malaria in southeast Asia is seriously jeopardised. Other ACTs are available, but each has limitations. One might anticipate that continued use of combinations including failing artemisinins will lead to the loss of one partner drug after another. New combination therapies that do not include artemisinins would be welcome, but the current pace of development suggests that no new chemical entities to treat malaria will be available for some years.[7] What should be done now?

Atul Loke/Panos Pictures

An interesting new strategy is triple ACT (TACT). The concept is simple: just add a third drug to an ACT. One might argue that this is a recipe to lose more drugs to resistance. Indeed, an axiom in the treatment of infectious diseases is to never add a single new drug to a failing regimen. But, perhaps axioms are meant to be broken, and the simple TACT concept might simply be a great strategy. TACT benefits from two key points. First, artemisinin resistance is not full-blown resistance; parasites with K13 mutations are eliminated by artemisinins, albeit more slowly than are wild-type parasites. Second, key ACT partner drugs have counteracting drug resistance mechanisms. The same transporter polymorphisms that mediate decreased sensitivity to amodiaquine and, to a lesser extent, piperaquine mediate increased sensitivity to lumefantrine and mefloquine.[8]

On the basis of this simple but compelling logic, a new multisite randomised controlled trial in *The Lancet* by Rob van der Pluijm and colleagues[9] has compared efficacies of three standard ACTs (dihydroartemisinin–piperaquine, artesunate–mefloquine, and artemether–lumefantrine) and two TACTs containing partner drugs with opposing resistance mechanisms (dihydroartemisinin–piperaquine plus mefloquine and artemether–lumefantrine plus amodiaquine) for the treatment of *P falciparum* malaria. The study design was complex, with different regimens studied in 1100 patients (median age 23 years [IQR 13–34], 854 [78%] male) with acute, uncomplicated *P falciparum* malaria alone or mixed with non-*falciparum* species in different regions of Cambodia, Thailand, Laos, Vietnam, Myanmar, Bangladesh, India, and the Democratic Republic of the Congo. The primary endpoint was efficacy, defined by 42-day PCR-corrected adequate clinical and parasitological response. The key results were straightforward. At sites where artemisinin resistance is not established, all regimens showed excellent efficacy, with tolerability and toxicity of the

TACTs similar to those of the ACTs. Most importantly, in regions of southeast Asia with relevant ACT resistance (Cambodia, Thailand, and Vietnam), 42-day PCR-corrected efficacies were 98% (95% CI 94–100) for dihydroartemisinin–piperaquine plus mefloquine versus a dismal 48% (39–56) for dihydroartemisinin–piperaquine. The study was limited by a lack of blinding and by a relative lack of paediatric participants, who are the highest risk group for malaria worldwide, but who make up a small proportion of malaria cases in areas with ACT resistance.

These new results suggest that TACTs might replace ACTs. The addition of mefloquine to dihydroartemisinin–piperaquine rescued the regimen from unacceptably poor efficacy, and mefloquine might additionally restrict selection of resistance to piperaquine. If safety and tolerability remain acceptable in follow-up studies, use of optimally dosed and formulated TACTs to treat *P falciparum* malaria might soon be appropriate in regions with artemisinin resistance. However, most cases of *P falciparum* malaria occur in regions without established artemisinin resistance. Should TACTs be implemented in these regions? On the one hand, TACTs might delay the development of resistance to multiple antimalarials, a vital benefit.[10] On the other hand, despite promising initial results, adding another drug to established regimens will likely add to challenges regarding tolerability, toxicity, and drug interactions, especially considering known concerns for the partner drugs mefloquine and amodiaquine.[11] On the ground, there might be little enthusiasm for changing highly efficacious regimens because implementing any policy change is difficult. Thus, this study offers promise for TACTs in regions with artemisinin resistance, but whether we should implement TACTs in other areas is uncertain. In any event, TACTs should be seen as a stopgap; novel combination therapies to treat malaria are greatly needed.

I declare no competing interests.

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Reducing malaria transmission with reactive focal interventions

A massive scale-up of investments in malaria control resulted in an estimated 663 million clinical cases averted in sub-Saharan Africa between 2000 and 2015,[1] and 11 countries have been certified malaria-free in the current millennium.[2] Unfortunately, progress has stalled recently, and increases in malaria incidence were observed in several endemic countries.[3] Continuing with business as usual is likely to jeopardise gains made in the past 20 years, and slow the progress towards elimination goals. Innovative and targeted measures are required to complement universal coverage with basic vector control and case management interventions, especially as heterogeneity in case incidence increases with declining transmission.

In the last mile to achieving elimination, malaria transmission and the appearance of asymptomatic and clinical infections become increasingly focal. Targeted reactive approaches, such as reactive case detection (RACD), are likely to form efficient interventions to eliminate infections and prevent onward transmission.[4] Supporting research on the effectiveness and operational

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