Potential of Artemisinin-Based Combination Therapies to Block Malaria Transmission

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(See the major article by Sawa et al on pages 1637–45.)

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At the end of the 19th century, Ross’s observations of parasites in the midgut of mosquitoes artificially fed on the blood a patient with malaria heralded the beginning of our understanding of the transmission of malaria and the dynamic interaction between the Plasmodium parasite and the Anopheles vector. The work by Ross and other early pioneers provided the rationale for aggressive control measures focused on reducing the access of mosquitoes to water, epitomized by major public health programs to drain marshes, and distribute bed nets. Early gains were boosted by major drug discovery programs during the Second World War and an expanding antimalarial pharmacopeia. Since 1945, 79 countries have eliminated malaria, with the proportion of the world’s population living in malaria-endemic regions falling from 70% to 50%. However, these achievements have been confounded by huge challenges, including the sustainment of major public health interventions, the propensity of plasmodia to evolve resistance to antimalarial drugs, and the ability of mosquitoes to evolve resistance to insecticides. The widespread use of partially effective treatment policies has had devastating consequences for malaria-endemic regions, resulting in a rising burden of morbidity and mortality.

Calls for a concerted action against multidrug-resistant strains of Plasmodium falciparum have coincided with a rising interest in the use of artemisinin derivatives. These compounds, derived from the leaves of the Artemisia annua plant, retain high efficacy even against multidrug-resistant parasites, providing a broad stage specificity of action and a faster clinical and parasitological response than any other known antimalarial agent. However, when artemisinin derivatives are given as monotherapy, their rapid elimination necessitates a prolonged course of treatment (minimum duration, 7 days) to achieve complete cure. For this reason, they are usually given in combination with a partner drug that has a long half-life, a strategy known as artemisinin-based combination therapy (ACT). The rationale for ACTs is that the short-acting but highly potent artemisinin delivers a rapid reduction in parasite biomass, with the remaining parasites being removed by the intrinsically less active but more slowly eliminated partner drug. The ACTs have an additional benefit of dramatically reducing the production of gametocytes, the sexual stage of the parasite [1], as a consequence of their rapid reduction in the parasite biomass, activity against the more mature asexual-stage parasites (the precursors of the sexual stages), and gametocytocidal activity against early gametocytes (stage I–III). Clinical studies confirm that patent gametocytemia is significantly reduced in patients receiving ACTs, compared with those receiving non-ACTs [2]. However, since transmission can occur in the absence of patent parasitemia, further confirmation of transmission potential requires membrane-feeding experiments and demonstration of reduced transmission and development in the vector itself. Together, the available evidence supports a key role for the ability of widespread deployment of ACTs to retard the emergence of drug resistance and reduce the morbidity of malaria in settings of low endemicity [3].

ACTs have now become an intrinsic part of the global antimalarial treatment policy endorsed by the World Health Organization and are deployed in >80 malaria-endemic countries. A variety of excellent alternatives are available, each with a slightly different profile of tolerability, adherence, availability, cost, efficacy, and effectiveness [4]. Of the newer combinations, artesether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DP)
are prime examples: both coformulations have been well tolerated with excellent efficacy in almost all studies conducted. However, these combinations differ in a number of aspects that may have important implications not only on the treatment of the patient, but also in their public health impact. A major difference is their duration of action: lumefantrine has a terminal elimination half-life of approximately 4 days, whereas piperquine has a terminal elimination half-life of 21–28 days. Suppressive concentrations of the drugs last approximately 16 days and 28 days, respectively. In addition, the artemisinin component and its dose differ significantly, with AL reliant on the lipophilic derivative artemether and DP reliant on the active metabolite and potentially less stable dihydroartemisinin.

The different pharmacokinetic profiles of the long-acting partner drugs have important implications for the posttreatment prophylactic properties of the regimens. The long-acting piperquine exerts a greater posttreatment prophylactic effect against reinfection and relapse than the more rapidly eliminated lumefantrine, resulting in a greater overall incidence of recurrent infections following AL therapy, compared with DP therapy [5]. In addition, the increased prophylactic effect afforded by DP allows a longer time for hematological recovery, which, in turn, reduces the cumulative risk of anemia [6].

There are also differences in the early parasite response, with AL frequently associated with a slower parasite clearance, compared with DP or mefloquine plus artesunate [7]. This may reflect the lower initial dose of artemether afforded by the twice daily dosing of the 6-dose AL regimen, compared with the once-daily dosing of most of the other ACTs. Paradoxically, although slower parasite clearance is usually correlated with increased gametocyte carriage [8], this was not apparent in the 14 published randomized studies of AL versus DP, in which gametocytemia in the DP arm was greater than that in the AL arm in 5 studies, less in 1 study, and similar in 8 studies. What is unclear is how these differences in treatment efficacy may affect the overall transmission potential of these 2 ACTs.

In this context, the well-designed and carefully executed study by Sawa et al in this issue of the Journal provides not only important data on the duration of gametocyte carriage but, for the first time, direct evidence of the transmission of malaria to the mosquito vector. In this comparative study, there was no significant difference in parasite clearance. Although the overall risk of recurrence was greater following AL treatment (21%), compared with DP treatment (3.7%), after PCR correction, both regimens had excellent efficacy (>97% by day 42). The number of gametocyte-positive days, determined by microscopic and molecular analyses, was 25% lower in patients treated with AL (32%), compared with those treated with DP (43%), but when carriage was present, the duration was significantly longer in the DP arm (mean duration, 15.3 days) compared with the AL arm (mean duration, 5.5 days). Although the proportion of patients infecting at least 1 mosquito was not significantly different between treatment arms, feeding on DP-treated patients was more likely to result in a greater number of oocysts in the mosquito.

The cause of these differences in gametocyte carriage is unclear but has been hypothesized to be a function of the lower total dihydroartemisinin dose in DP (4.8–9.9 mg/kg), compared with that of artemether in AL (9.6–13.2 mg/kg) [9]. The study was conducted in an area of moderate transmission in western Kenya, which may have increased the likelihood of gametocyte production at presentation (gametocytes were present in 10% of patients at presentation), thereby enhancing any difference in the gametocytoidal properties of the regimens. However, the greatest benefit of the transmission-blocking properties of ACTs is likely to be in low-transmission settings, where a greater proportion of parasitemic patients receive treatment and gametocytogenesis can be prevented before it begins.

Importantly, the article is a reminder that despite excellent efficacy, significant differences in the therapeutic response can exist between ACTs. These properties deserve close scrutiny, particularly with the emerging threat of artemisinin resistance now present in Southeast Asia [10]. It emphasizes the need for amimalarial clinical trials to report gametocyte carriage in a standardized and comparable way, as well as the importance of mosquito-feeding experiments, at which the authors excel, to provide complementary data on the whole transmission cycle. However, what the study was unable to address was the public health implication of these observed differences. The authors acknowledge this and, indeed, call for longitudinal studies over repeated reinfections to confirm the payoff between greater the posttreatment prophylaxis of DP and the gametocytoidal properties of AL. Alternatively, cluster-randomized community studies would be needed, allocating communities to one therapy or the other.

The study also reminds us that despite their huge potential to reduce transmission, ACTs cannot be relied on to prevent it altogether, a property not just leveled at DP. New approaches have been proposed, including coadministration of ACTs with primaquine (a drug with broader gametocytoidal properties than the artemisinins), and these have been shown to produce a substantial reduction in gametocyte carriage, compared with ACTs alone [11]. Indeed, in one study conducted in Myanmar, the administration of a single dose of primaquine with ACTs resulted in no difference in gametocyte carriage between DP and any of the other ACTs tested [12]. Optimizing the use of the tools at hand and designing better combination therapies will help increase the impact of treatment policy, not only for patients being treated, but also for the wider community of at-risk individuals.
Note

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