Once-Daily Combination Therapy for Uncomplicated Malaria: Is This the Way Forward?

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(See the article by Ashley et al. on pages 425–32)

There are several problems associated with treatment of malaria, especially in sub-Saharan Africa: effectiveness, access (financial and physical), safety and tolerability, and adherence. Even in an ideal situation in which the first 3 factors are not a problem, adherence would still be problematic, especially when dealing with rural populations in developing countries, where relief of symptoms of malaria is often interpreted as "cure" and where there is, therefore, great reluctance to continue taking the rest of the medication as prescribed. Adherence has been defined as "the extent to which a patient fulfills the intention of the prescriber in taking medication" [1, p. 7]. Several drug-associated factors may affect adherence [1], including appropriateness of the prescription, side effects, dose regimen, drug presentation and formulation, number of drugs prescribed concurrently, and duration of treatment.

Adherence to antimalarial drugs has been shown to be better with effective treatments, coupled with increased knowledge by the health care professional, better medication packaging, and provision of correct dosages [2]. Combination therapy, especially that which contains artemisinin derivatives (ACT), is now accepted as the way forward in confronting the serious problem of drug-resistant *Plasmodium falciparum* malaria [3]. Combination therapy has the potential to improve therapeutic effectiveness, delay spread of drug resistance, and reduce gametocyte carriage [4]. ACTs need to be given for at least 3 days to maximize the number of parasites killed. Because adherence is a critical component of the overall effectiveness of a drug [5], complicated dose regimens are bound to compromise effectiveness through reduced adherence. The simplest ideal dose regimen for ACTs would involve once-daily administration for at least 3 days. A few studies have reported on the efficacy of and/or adherence to such "once-daily" ACTs, but some of the results are conflicting. For example, one study of a relatively simple regimen (a single dose of sulfadoxine [equivalent to 25 mg per kilogram of body weight] on the first day, and 4 mg of artesunate per kilogram of body weight daily for 3 days) that was performed in a refugee camp in Zambia reported that up to 50% of the patients were nonadherent [6]. In a separate study performed in the same camp, the authors reported a significant difference in therapeutic response to the same combination between patients who received either supervised or unsupervised treatment, a fact attributed to insufficient patient adherence in the unsupervised group [7]. In contrast, in another study, 90% of patients in southwestern Uganda were reported to be adherent to the more complicated 6-dose regimen of artemether-lumefantrine for treatment of uncomplicated malaria [8]. There is need for more comparative studies on the efficacy of and adherence to simple regimens of ACTs for treatment of uncomplicated malaria.

In this issue of *Clinical Infectious Diseases*, Ashley et al. [9] describe the results of a randomized trial comparing a simple, once-daily dose of dihydroartemisinin-piperaquine administered over 3 days (DP3) with the standard but more complicated regimen of an equivalent total dose of the same combination given in 4 doses over 3 days (DP4) and with a once-daily dose of mefloquine-artesunate administered over 3 days (MAS3) for the treatment of multidrug-resistant falciparum malaria. Fever and parasite clearance rates were similar for the 3 regimens, whereas PCR genotyping–adjusted cure rates were 99.4%, 100%, and 95.7% for the DP3, DP4, and MAS3 groups, respectively, 63 days after starting therapy. Given the level of parasite resistance in the study area, the results with DP3 are encouraging. This simple regimen could even be used in situations in which adherence is generally

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problematic. For example, the first dose on day 0 could be administered under supervision at the health facility, and even the patients who are most likely to be noncompliant would presumably adhere to the 2 doses remaining in the regimen.

Although malaria transmission rates vary widely in sub-Saharan Africa, the majority of susceptible people live in areas with rates that are higher than that in Southeast Asia. For example, the entomological inoculation rate (EIR), which measures the number of infective mosquito bites per person per period, has been reported to be 0.3 infective bites/person per year in Tak Province, Thailand [10]. In contrast, in some parts of Africa, the EIR has been estimated to range from 0.001 to 2.7 infective bites/person per night [11, 12]. This factor, plus the differences in the level of parasite resistance between Southeast Asia and sub-Saharan Africa, makes it difficult to interpret the results presented by Ashley and colleagues in the context of potential use of the DP3 regimen in sub-Saharan Africa and other areas with different malaria ecologies. Thus, although the results reported by Ashley et al. [9] are encouraging, there is a need to perform similar trials of DP3 and other "once-daily" regimens, especially in sub-Saharan Africa. Such trials would be especially timely, given that several countries in sub-Saharan Africa have switched or are in the process of switching to Coartem (artemether-lumefantrine; Novartis) as the recommended first-line treatment for uncomplicated malaria. The treatment regimen with this drug is more complicated and, presumably, will be associated with more problems of adherence than equally effective but simpler "once-daily" regimens. Taken together with results presented by Ashley and colleagues, the results of similar studies in sub-Saharan Africa will help clarify whether these simple, once-daily, 3-day regimens are the way forward in the treatment of uncomplicated malaria.

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