To the Editor—The evolution of widespread resistance to chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) in Africa has required the urgent introduction of new antimalarial therapies. The World Health Organization now considers it mandatory that replacement antimalarial therapies be deployed as combination therapies (CTs) [1]; and those CTs containing artemisinin derivatives are currently among the most popular. Experience with mefloquine and artesunate in Southeast Asia has been used to argue that combinations with unmatched pharmacokinetics (i.e., a short–half-life artemisinin and a long–half-life partner drug) are the preferred option. This argument has been made despite concerns that mismatched pharmacokinetics allow parasites to evolve resistance sequentially as the longer–half-life partner persists as a vulnerable monotherapy (figure 1), a result that can almost completely undermine the benefits of CT [2, 3]. Coartem (the Novartis brand name for the artemether-lumefantrine combination) was one of the first CTs to be deployed, and field data provided by Sisowath et al. [4] have provided the first indications of its likely fate. They showed that parasites carrying the 86N mutation can infect people immediately after artemether treatment, whereas parasites carrying the 86Y mutation can infect people 17 days posttreatment. The drugs have decayed to nontherapeutic levels when they cross the X-axis (defined as the concentration at which the drug, if present as a monotherapy, would be unable to prevent infection by drug-sensitive parasites). The pfmdr 86N mutation’s (orange arrow) increased tolerance of lumefantrine allows it to infect a person 17 days posttreatment, compared with 30 days posttreatment for the 86Y mutation. Two scenarios are given for subsequent mutational steps. Scenario 1 is a single large increase in drug tolerance (red arrow), in which the presence of artemether in the CT is powerless to stop the spread of this mutation, whose increased tolerance of lumefantrine allows it to infect a person 4 days posttreatment and to spread through the parasite population, displacing the 86N form, which can infect no earlier than 17 days posttreatment. Scenario 2 is a subsequent increase in tolerance, which occurs as a series of small increments (black arrows); the presence of artemether in the CT will slow this process when it reaches day 4, and Coartem may remain clinically effective for a longer period.

On the basis of the data shown in table 1 of the article by Sisowath et al. [4], we can estimate the increase in tolerance of Coartem. Infections carrying the 86N mutation start to appear by days 26–28 posttreatment. Coartem does not affect the initial hepatic stage of a falciparum malaria infection, so, if we assume that 10 days elapse between the parasite’s emergence from the liver and the subsequent red blood cell (RBC) infection becoming patent, the implication is that an RBC infection carrying the 86N mutation can infect people ∼17 days after the start of treatment. The 86N and 86Y mutations have returned to their normal proportions by approximately day 40, so the estimated time until the 86Y mutation can reinfect is ∼30 days; this is illustrated in figure 1.

The factor that will determine the fate of Coartem therapy is the size of the drug–tolerance increase(s) encoded by the next mutation(s), which need not be in the pfmdr gene; if this increase is large, as indicated by the red arrow in figure 1, then the long-term future of Coartem therapy is in extreme jeopardy. Parasites carrying this mutation will spread because they can infect people immediately after artemether has decayed to subtherapeutic levels—that is, by approximately day 4 after the start of treatment. The clinical question, then, is whether Coartem therapy will reliably eradicate infections carrying this mutation. Field data on other drugs suggest that this is doubtful: adding a 3-day regimen of artesunates to drug treatments that are already failing has increased clinical cure.
rates by only 50% [5, 6]—an unacceptably small impact, given that resistance to lumefantrine will continue to spread—and so future Coartem therapy would appear to be distinctly vulnerable in an African setting. (This finding is of particular concern in Coartem therapy, whose regimen of 6 doses, of 4 tablets each, given over a 3-day period may result in poor compliance.)

A further concern is the speed with which these mutations were selected. Coartem has already resulted in their selection, despite its having been deployed only recently, as a second-line drug, in the study area (the mutations were presumably already present at significant frequencies, probably because of local use of structurally related antimalarial therapies). Furthermore, the 86N mutation appears to substantially increase the tolerance, by a factor equivalent to 50% of lumefantrine’s time of persistence (figure 1). The saving grace may be that, at least in the case of CQ and SP, mutations affecting tolerance/resistance occur extremely infrequently and, depending on their origin, may be further slowed by CT [7]; consequently, the timescale for the final evolution of resistance remains unclear. The timescale may be largely determined by chance (see figure 2 in the article by Hastings [7]); however, it does appear plausible, even likely, that we are 1 mutation away from clinical resistance to Coartem—and that we are currently trusting to luck, with all that that implies for the future deployment of CTs in Africa. Furthermore, the current situation arose almost immediately after Coartem was first deployed; however, this should not be interpreted as a reason to delay substitution of a CT for a failing antimalarial monotherapy, because this strategy remains our best hope for a long-term treatment. However, the unambiguous message of these studies is that CTs are not a panacea and that they may have a limited therapeutic life span. The first recommendation that needs to be considered is that CTs with better-matched elimination rates should be developed, probably by using a partner drug that does not persist as long as lumefantrine.

The second recommendation is that formalized mechanisms for the monitoring of resistance should be considered to be essential, to provide early indications of problems, thereby enabling the long-term strategic planning necessary to obtain the maximum benefit from CT.

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Note added in proof. The World Health Organization is now reporting that Coartem has clinical failure rates of 13%–30% in Cambodia (http://www.who.int/malaria/rbm/Attachment/20041108/Drugefficacybycountry.pdf).

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Reply to Hastings and Ward

To the Editor—Hastings and Ward’s comments [1] on our recent publication concerning Coartem’s (the Novartis brand name for the artemether-lumefantrine combination) in vivo selection of the pfmdr1 86N mutation by [2] are a worthy contribution to the discussion of our find-
ings. In particular, we welcome the concept of “tolerance” as an operational complement to “resistance” [3, 4]. However, we believe that their comments require some further clarification with regard to the use of artemisinine derivative–based combination therapy (ACT) in Africa.

We also agree that the success of chemotherapy strategies in high-transmission areas in Africa will be dependent on the pharmacokinetic characteristics of the drugs employed [3]; and lumefantrine actually has a relatively favorable profile when compared with other quinolines. But we also want to highlight the importance of the possible mode of resistance in the parasite. Consider the example of the chlorproguanil-dapsone combination: although its components have relatively short and similar half-lives (17–30 h and 23–70 h, respectively), the simple mechanism of resistance based on modification of the drug’s target (the dehydrofolate reductase enzyme) allows the relatively rapid selection of parasites carrying particular pfdhfr mutations [5]; indeed, selection of 1 pfdhfr mutation, 1164L, has also been recently suggested by the results of studies of treatment with a similar combination, proguanil-dapsone, even when the latter is combined with...