P. lucinski and colleagues (1) recently published the results of a therapeutic efficacy study of artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DP) in Zaire and Uige Provinces in Angola and concluded that there was evidence of increased lumefantrine resistance in Zaire. It is our opinion that this conclusion is not supported by the data presented.

We applaud the authors for their efforts to monitor for potential antimalarial resistance in Angola. However, we would like to note a number of limitations of the study, several of which were also acknowledged by the authors.

The study was not randomized, and participants were enrolled at different times in the transmission season: the AL arm was enrolled during a period of high transmission, and the DP arm was enrolled later and during a period of lower transmission. Thus, the risk of reinfection, and misclassification as treatment failure, would be higher for the AL cohort than for the DP cohort.

In context, we stress that reinfections are not treatment failures, though these terms were used interchangeably in the text. Reinfec tions are new infections after the drug treatment course has finished and happen more often during periods of peak malaria transmission. Treatment failures are recrudescent infections where the original infection was not eliminated or cured with the course of drug treatment.

AL must be administered with food to increase the absorption of lumefantrine (2, 3). Conversely, DP should be taken in a fasted state. The authors do not comment on whether these guidelines for dosing were followed. Notably, half of the AL doses were taken without supervision at home, raising the possibility of missed doses or loss of dose through vomiting. Thus, lack of compliance with dosing guidelines for AL and consequent subtherapeutic exposure might explain some of the lack of efficacy in this arm. This issue could have been resolved by measurement of plasma lumefantrine concentrations, which should be performed in future studies to definitively assess AL efficacy. The day 7 plasma lumefantrine concentration provides a simple measure of drug exposure that correlates well with the AL therapeutic response (2, 4–6).

As noted by the authors, parasites with the NFD or NYD haplotype may need higher blood lumefantrine concentrations than chloroquine-resistant parasites with the Y86, F184, and Y1246 haplotypes.

In vitro sensitivity testing of patient parasite samples would have been helpful to determine the loss of susceptibility, if any, to artemether or lumefantrine. The Pfdmrd1 allele, which has amino acids NFD or NYD at residues 86, 184, and 1246, respectively, has not been associated with treatment failure in African countries. These alleles are typically thought of as wild-type sequences and do not lead to lumefantrine resistance, as the authors suggested, nor do they cause “in vivo lumefantrine tolerance,” as others had purported (7). While the chloroquine-resistant Pfdmrd1 YFY allele (Y86, F184, and Y1246) is associated with a significant increase in lumefantrine potency over wild-type, parasites bearing the NFD and NYD wild-type alleles are nevertheless fully susceptible to the lumefantrine exposures achieved when AL is administered in accordance with approved labeled dosing.

The authors note that there is a significant difference in the efficacy of AL between the two provinces, suggesting that rates of lumefantrine resistance might be higher in Zaire than in Uige Province. However, other possibilities could explain this observation. First, the prevalence of parasites with the chloroquine-resistant Pfdmrd1 YFY allele might be higher in Uige than in Zaire; second, there might have been a higher rate of reinfection in the AL arm in Zaire than in Uige; and third, 17% of the children treated with AL in Zaire had high parasitemia levels (>100,000 parasites/ml) compared to 5.2% in Uige (Table 1 in reference 1), which could have been associated with an increased risk of failure due to a greater parasite burden. These caveats, combined with the potential for subtherapeutic dosing of AL at home, prevent any conclusion on the frequency of lumefantrine resistance at either study site.

It is critical to monitor the potential development of resistance to current front-line antimalarials such as AL, as the authors have attempted to do. Careful surveillance of clinical efficacy, genetic changes in the parasite, and in vitro activity of artemether and lumefantrine remains an urgent priority.

REFERENCES
