

Artemisinin-Based Combination Treatment for Malaria in Africa: No Perfect Solutions

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(See the article by Mårtensson et al. on pages 1079–86)

Drug-resistant malaria is one of the major public health challenges facing Africa. The spread of resistance to chloroquine and subsequently sulfadoxine pyrimethamine (SP) means that the era of inexpensive monotherapy for malaria is passing or has passed. There is widespread acceptance that a combination of ≥ 2 antimalarial drugs should now become standard treatment policy, as it is for tuberculosis and HIV infection. There has been a strong push, which has sometimes run ahead of the evidence, to encourage countries in Africa to adopt artemisinin-based combination treatment (ACT) as first-line treatment for uncomplicated malaria as soon as possible. The decision that drug combinations should be used in principle is one thing; the decision about which combinations to use and how they are best deployed is quite another. A number of practical questions remain unanswered for countries looking to implement ACT, including questions about the effectiveness, safety, availability, and, importantly, cost of new drugs. The cost of ACTs is ~ 10 times that of current monotherapy, and it is currently unclear how ACTs can be used

on a wide scale in Africa without substantial and sustained subsidization [1].

Most countries in Africa using ACTs are currently choosing between artemether-lumefantrine (AL) and artesunate plus amodiaquine (ASAQ; not currently co-formulated). In this issue, Mårtensson and Strömberg et al. [2] report a carefully conducted study in Zanzibar, Tanzania, comparing the efficacy of these combinations in children followed up for 42 days. Both the extended follow-up duration and the region in which the investigation was conducted make this an important study. Many countries in Africa have, in principle, decided to adopt ACT as standard treatment for malaria, but only a few have actually made that change in practice. Zanzibar—with financial support from the Global Fund to Fight AIDS, Tuberculosis, and Malaria—was one of the first to change, choosing a combination of ASAQ as first-line therapy and AL as second-line therapy for patients for whom treatment with ASAQ failed.

In the face of increasing rates of drug failure with monotherapy, Zanzibar adopted ACTs as standard treatment for malaria before reliable data on the efficacy or effectiveness of these particular drug combinations could be collected locally. The current trial provides the efficacy data to support that change, albeit after the change has been made. This is not trivial; the assumption that ACTs are always more effective than alternative treatments is not

always true. Addition of artemisinins to a locally failing drug leads to an ineffective combination [3, 4], and combinations of older drugs, which are generally cheaper, have proved to be as effective as ACTs in some settings in east Africa [5]. Because ASAQ is cheaper than AL, Zanzibar's approach seemed likely to be more cost-effective than using AL for all cases of malaria. On the other hand, amodiaquine was widely used in Zanzibar before the policy change, and amodiaquine resistance is prevalent in mainland Tanzania. In settings where amodiaquine resistance is high, the ASAQ combination has relatively high failure rates. Therefore, there was no guarantee that the ASAQ combination would be effective [4].

The strength of this study is that it compares locally relevant drug combinations in a randomized trial for a prolonged period with minimal loss to follow-up. In areas of high malaria endemicity, assessment of antimalarial drug efficacy has typically been limited to the 14 days following treatment, because of the high likelihood of reinfection and the difficulty in distinguishing recrudescence due to treatment failure from reinfection. The need to extend the follow-up period to ≥ 28 days to avoid underestimating the true risk of treatment failure has been recently recognized and supported by the use of genotyping to distinguish between cases of recrudescence and reinfection. The prolonged follow-up period in this trial is jus-

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tified by the significant rate of recrudescence that continued after day 28, particularly in the AL arm. However, the overall cure rate by day 42, which was significantly different between the arms (56% in the ASAQ group vs. 77% in the AL group), largely reflects a difference in the rate of reinfection, rather than the rate of recrudescence. By follow-up day 42, the true PCR-adjusted rate of recrudescence was ~10% in each arm, with a small but statistically nonsignificant advantage for AL.

There has been debate about whether the overall cure rate or the PCR-adjusted true recrudescence rate is more useful, and this study highlights the importance of the difference. In practice, both have merits. For the individual child or family, an additional episode of malaria is the same, whether it is reinfection or recrudescence. Assertions that reinfection is in some way more dangerous than recrudescence at an individual level are generally unsupported by data from Africa [6]. Viewed this way, the trial is sobering reading: even with these expensive drugs, between one-quarter and one-half of all children with an attack of malaria in a high-transmission setting have detectable parasites within 6 weeks after treatment, and most are likely to go on to develop symptoms.

At a public health level, the difference between recrudescence and reinfection is potentially important. If 2 drug combinations have a similar rate of recrudescence but 1 provides prolonged protection, in areas of high transmission, there are arguments for and arguments against the appropriateness of using the drug with longer activity. On the positive side, protecting a child who has had an attack of malaria from a subsequent episode may give them time to make a full clinical recovery. On the other hand, with any ACT, the prophylactic effect after treatment will always be provided by the non-artemisinin companion drug because of its longer elimination half-life. A prolonged period in the blood as monotherapy means that there is at least a theoretical increase in the vulnerability of the drug to developing

or spreading resistance. There is some evidence, albeit small in scale and very indirect, that resistance may have developed to lumefantrine in this trial. It is therefore unclear whether a short-acting or long-acting companion drug for artemisinins is preferable.

This trial has some limitations. One limitation is the difference in the lower age limit for enrollment between the 2 arms. Older children are likely to have increased immunity may have lower rates both of reinfection and of recrudescence, compared with younger children. If so, this would favor the use of AL. The fact that adding age data to a regression model strengthened the advantage of AL is reassuring but does not exclude the possibility of bias; analysis restricted to children of the same age would have been even more convincing. A second limitation is that the trial was not blinded. The lack of blinding could have impacted the assessment of efficacy, and more likely, adverse events. It is a generic limitation of efficacy trials that, because all doses are observed, such trials are likely to overestimate the effectiveness of drugs used under normal conditions. The dosing regimens for both combinations are complex, although recent evidence suggests that, when AL is administered in the packaging designed by the World Health Organization, adherence is generally good. An effectiveness trial comparing AL with ASAQ conducted on the mainland of Africa just opposite of Pemba found an even greater advantage for AL [7], but it is not possible to say whether lower adherence or greater resistance to amodiaquine was the primary reason for this difference.

Although ASAQ and AL have been recently adopted by many countries, each has limitations. The longevity of ASAQ may be limited by underlying resistance to amodiaquine, and the current lack of coformulation of ASAQ may reduce adherence. The comparatively higher cost of AL could have a substantial impact on drug availability, distribution, and sustainability. Thus, neither regimen is a perfect

solution, and other (preferably significantly cheaper) drugs are needed.

The choice of an efficacious and safe drug is only the first of many tasks facing policy makers and clinicians who wish to use ACTs to treat malaria. If ACTs are to be used effectively, more data are needed, particularly from studies covering multiple episodes of malaria and studies evaluating the cost-effectiveness of these drugs in settings where diagnostic facilities are limited and most episodes of malaria are treated outside of the formal sector. Zanzibar, one of the earliest adopters of ACTs in Africa, provides an opportunity to start to examine these difficult practical questions.

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