Enthusiasm for using artemisinin-containing combination therapy (ACT) for the treatment of falciparum malaria has been growing dramatically. Pressure on African governments to move quickly to use ACT has been growing as well. In April 2001, the World Health Organization strongly endorsed the use of combination therapy, especially ACT, in Africa. Several African countries have adopted ACT for at least part of their territory. South Africa adopted artemether-lumefantrine for KwaZulu Natal and Zanzibar adopted artesunate-amodiaquine (Abdulla S, personal communication). The enthusiasm has reached such heights that to suggest any course of action other than ACT approaches heresy.

Briefly, there are three promised benefits of ACT: high and rapid parasitologic cure rates; potential inhibition of development of drug resistance; and reductions in overall malaria transmission rates. Experience in Southeast Asia suggests that, at least in that environment, ACT (mostly artesunate-mefloquine) has proven to be a highly efficacious and durable malaria treatment and has at least contributed to substantial reductions in malaria morbidity and mortality in the region.

Why, then, would Gasasira and colleagues in Uganda study a combination of sulfadoxine/pyrimethamine (SP) and amodiaquine (AQ)? In a world that has accepted the demise of both chloroquine (CQ) and SP in Africa, even if somewhat prematurely, and is now racing headlong towards ACT, isn’t this study just a bit anachronistic? Why should we pay attention?

The reason is that, while ACT undoubtedly holds tremendous promise as a malaria treatment, the reality of ACT today is somewhat problematic.

One problem is availability. Substantial quantities of quality artemisinin drugs are actually hard to come by. Producers have been reluctant to invest in very large-scale production of *Artemisia annua*, the source of artemisinin drugs, when the actual market for the product is presently small and there remains some uncertainty about how big and how fast it will grow in the future. A lag time of 2 to 3 years might be needed for supply to meet a sharp increase in demand.

A second problem is cost. ACT is far more expensive than currently used treatments and more than most African economies can sustain. The advent of the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM) has made available considerable financial resources that could be used to buy ACT. Unfortunately, concern over the long-term viability of the GFATM has already been raised. Additionally, no one has figured out, even with GFATM support, how to make such expensive drugs affordable through the private sector pharmacies, drug shops and kiosks that are used so extensively in sub-Saharan Africa.

A third problem is efficacy. First generation ACTs are co-administrations of an artemisinin (ART) compound with an existing malaria drug, such as SP, AQ, CQ, or mefloquine. Experience in Africa with most of these drugs in combination with ART is not inspiring: when the partner drug’s efficacy is low, the efficacy of the combination is greatly compromised (Obonyo C, personal communication). Substantial increases in efficacy will require partnering ART with less widely used drugs or truly novel drugs, such as lumefantrine, proguanil-dapsone, or piperaquine.

A fourth problem is dosing complexity and other use characteristics. Most currently available ACTs must be co-administered as separate pills, greatly increasing complexity of treatment and chance of misuse. With the exception of artesunate-lumefantrine, co-formulated combinations of more truly novel compounds (second generation ACT) are still 2 to 3 years away or more. Even though coformulated, artesunate-lumefantrine is still a complex regimen (4 tablets twice daily for 3 days for an adult) and compliance, and therefore programmatic effectiveness, is likely reduced.

Finally, there is limited experience in sub-Saharan African countries with ACTs. At a time when senior clinicians in the country may not have any experience with such drug combinations, it may be challenging to implement a policy for using such drugs in homes and peripheral clinics for first line therapy of fever illness. Antimalarial drug policies have often introduced a new drug on a limited basis for use after the standard drug fails, or for use in hospitalized patients where experience can be gained, safety and tolerance can be better understood, and confidence in it can be gained. This may especially be needed with some ACTs where the safety of the combination is essentially unknown, especially for the highest risk groups of very young children and pregnant women.

So, what do these problems have to do with SP+AQ? Many African countries are in the unenviable position of having current treatment strategies (either CQ or SP monotherapy) that are in need of change. But what do they change to? For the reasons outlined above, currently, the decision on which ACT to choose is not at all clear. Adoption of ACT now would entail substantial increases in drug costs at a time when it isn’t clear just how these costs would be sustained, especially within the private sector where they are needed most.

SP+AQ is probably not a perfect option; however, a perfect option doesn’t exist. It won’t work everywhere - this combination has been studied elsewhere in Africa with variable success (Kazadi W, personal communication). SP+AQ may not have the added benefits associated with ACT, such as transmission reduction and resistance inhibition, but then these characteristics are still only theoretical in the context of African malaria. But where SP+AQ can be shown to be acceptably efficacious, why not consider using it?

Is this a case of “cheap drugs for poor people”? No, this is a case of pragmatic decision making at a time when there are no clearly superior options. No one is advocating using drugs that don’t work. But, if in specific environments, SP+AQ is shown to work as well as other options, should countries ig-
nore it just because it isn’t an ACT? Should it be ignored when many of the reported benefits of ACT are still unproven in Africa and many of the problems with implementing ACT have not yet been worked out? Within 3 to 5 years, there may well be more affordable second generation ACTs available that solve this dilemma, but right now, can African countries afford to overlook effective strategies because they do not fit the popular notion of what should be done?

Many African countries are in a holding pattern of “interim policies” using less than ideal monotherapies or combinations (such as Uganda’s first line policy of SP+CQ). Investigators in Uganda have shown in this study and others that SP+AQ is not only better than SP, AQ, and SP+CQ, but also, in this environment, as good or better than ACT.¹¹,¹² Many African countries are already using either SP or CQ for the treatment of malaria with AQ or SP as second line treatment, respectively. Moving to SP+AQ would not be terribly difficult for most of these countries and might offer an effective, affordable, and available, and perhaps even reasonably durable, interim policy while they ponder how to approach ACT, hopefully, for the longer term.

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