Artemisinin Combination Therapies and Malaria Parasite Drug Resistance: The Game Is Afoot

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(See the major article by Conrad et al on pages 344–53.)

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Artemisinin therapies for malaria are a revolutionary medical advance [1]. Derivatives of artemisinin are highly effective killers of malaria parasites and reduce Plasmodium falciparum densities in a log-linear fashion. They are therefore first-line therapy for uncomplicated and severe falciparum malaria across the globe [2]. For uncomplicated falciparum malaria, treatment typically entails a short course of an artemisinin derivative coformulated with a partner antimalarial as artemisinin combination therapy (ACT); in 2013, these ACTs were administered in >330 million courses globally [3].

ACT resistance would imperil malaria control. Consequently, sophisticated efforts are under way to quantify and track parasite susceptibility both to ACTs and to artemisinins themselves. In recent years, parasites in western Cambodia have cleared progressively more slowly from the blood after artemisinin therapy, a finding considered to be a potential early sign of artemisinin resistance and a harbinger of clinical failures [4]. To better detect these parasites, this phenotype has recently been associated with several polymorphisms in a novel parasite gene [5], and coordinated efforts are under way to track, contain, and eliminate these artemisinin-resistant parasites before their export from Southeast Asia. These efforts are critical, and it is imperative that efforts to sustain the longevity of ACTs do not overlook the importance to parasite killing of the artemisinin partner drugs.

In this issue of The Journal of Infectious Diseases, Conrad and colleagues employ a novel study design to investigate the impact of the choice of ACT upon parasite resistance to the artemisinin’s partner drug. To do so, the investigators randomized Ugandan children to receive 1 of 2 ACTs: artemether-lumefantrine (AL) or dihydroartemisinin-piperaquine (DP). Because artemether is rapidly converted to dihydroartemisinin, the essential difference between study groups was the partner drug: lumefantrine or piperaquine. The notable innovation of their study was the continued administration of the assigned ACT for all subsequent episodes of malaria (about 5 episodes per year) and the follow-up assessment of markers of resistance to the partner drugs at regular intervals over 5 years. This innovative study design more closely replicates antimalarial use in the real world and allows for a more careful measurement of the impact of ACT policy upon the promotion of resistance to partner drugs.

In their study, both regimens were highly efficacious, with treatment failure rates of <1%. In the serial analyses of parasite mutations, alleles that decrease lumefantrine susceptibility increased in frequency in both groups over time; this was likely promoted by AL use in the wider, nonstudy population. Interestingly, however, the rate of increase in these alleles was slower in the children randomized to DP compared with those receiving AL. Supporting this observation were the genotypes of parasites acquired after shortly after AL or DP treatment, when the artemisinin derivative will have been completely removed from the serum in significant concentrations. These observations implicate the widespread use of AL for the increase in allele prevalence that reduces parasite susceptibility to lumefantrine. Interestingly, these data also suggest that this selective pressure was partially mitigated by...
DP. Parasite genotypes from the 2 study groups in infections occurring shortly after therapy with AL and DP showed opposing selection: Broadly speaking, DP selected for AL-sensitive parasites and AL selected for DP-sensitive parasites. Therefore, in the overall population of malaria parasites, AL and DP applied antagonistic selective pressure on drug resistance genotypes.

This finding has several important implications. First, this is the first evidence from a population-based study that piperaquine selects for known drug resistance polymorphisms in malaria parasites. This observation enables improved surveillance for resistance to DP, which is used widely in Southeast Asia and has been considered for wider use in Africa. Second, as the authors suggest, the antagonistic selection of parasite genotypes by these 2 regimens suggests that the spread of resistance to partner drugs may be forestalled by policies that promote alternate effective first-line therapies. Such treatment algorithms are not new; for many years, antibiotic rotation in intensive care units has been investigated as a tool to limit antibacterial resistance. For malaria parasites specifically, this approach is grounded in the marked resurgence of chloroquine susceptibility in Malawi that resulted when chloroquine use was restricted in the 1990s [6], suggesting that cycling of antimalarials may prolong their useful lifespan. In addition to cycling antimalarials sequentially, the concurrent use of several first-line ACTs in parallel may also forestall resistance, as predicted in some mathematical models [7]. The safe and effective employment of these policies will require monitoring similar to that carefully achieved herein by Conrad et al.

Moreover, this study underscores the fundamental importance of the partner drugs in ACTs. Current treatment guidelines fail to adequately dose artemisinin drugs to clear parasites from uncomplicated malaria infections. In these infections, 7 days of artemisinin monotherapy fails in nearly 25% of patients [8]; nevertheless, guidelines recommend only 3 days of ACT. These shorter regimens undoubtedly enhance adherence to complete courses. They also, however, render the artemisinin component insufficient to clear parasites and therefore reliant upon the assistance of the partner drug for parasite killing. Importantly, while artemisinin derivatives have plasma half-lives of <3 hours, these partner drugs are cleared from the blood much more slowly, with half-lives between 5 days (lumefantrine) and 5 weeks (piperaquine) (Figure 1). A consequence of this ACT design is that, following a phase of rapid but incomplete parasite killing that is chiefly mediated by the artemisinin component, the partner drug removes residual parasites while functioning as monotherapy. During this phase, the success of ACT is dependent upon the partner drug alone. Not surprisingly, ACT failures have been blamed on resistance to the partner drugs sulfadoxine-pyrimethamine in Uganda [9] and Kenya [10] and mefloquine in Cambodia [11, 12].

Because of this approach to ACT design, it is clear that, far from being the sidekick or understudy to the artemisinin drug, these drugs are true antiparasitic partners: If artemisinin is personified by the quicksilver Sherlock Holmes in its pursuit of malaria parasites, the partner drug is the slower, prosaic Dr Watson of ACT, rarely grabbing headlines but critical to the job. Therefore, it seems prudent to complement surveillance of artemisinin resistance with that for partner drugs. As noted above, the study by Conrad et al describes novel associations between piperaquine and parasite drug resistance mutations, but for several other partner drugs the molecular markers of resistance are well described: Drug susceptibility is partly mediated to lumefantrine and amodiaquine by mutations in the P. falciparum dihydrofolate reductase (pfmdr1) and P. falciparum chloroquine resistance transporter (pfcr) and P. falciparum multidrug resistance gene (pfmdr1) and to sulfadoxine-pyrimethamine by mutations in the parasite’s dihydrofolate reductase (dhfr) and dihydropteroate synthase (dhps) genes. Currently, 1 of these 4 drugs is partnered in an ACT that is recommended as first-line therapy for uncomplicated malaria in 55 African countries.

Future studies and surveillance systems can employ the markers we currently possess for rapid surveillance of resistance as well as investigate—as Conrad
et al have done for piperaquine—the emergence of new drug resistance associations. Given the universal use of ACTs, their critical importance to malaria control, and the existing and emerging understanding of the molecular markers of resistance to both artemisinins and their partner drugs, this seems elementary.

Notes

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References