

Can we improve drug efficacy by taking parasite rhythms into account?

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The spread of malaria parasites resistant to the most common antimalarial drugs, the artemisinins, is of increasing concern. With few alternative drugs available, the therapeutic lifespan of artemisinins should be maximised. Current treatment regimens do not consider the rhythmic replication of *Plasmodium* parasites during their intra-erythrocytic development cycle (IDC). For example, artemisinin combination therapy of *P. falciparum* often covers 3 days, the equivalent of 1.5 IDCs. Daily doses of the short-acting artemisinin component would alternate targeting early (rings) or late (trophozoites) developmental stages. Depending on the parasite stage present at the start of treatment, either the less sensitive rings or the more sensitive trophozoites are targeted twice. We used the rodent malaria, *P. chabaudi*, to test whether a 4-dose regimen covering 2 IDCs can not only improve artemisinin efficacy compared to a 3-dose regimen, but also decrease variation in treatment outcomes with respect to the stage present at the start of drug treatment. Whilst chronotherapy may improve treatment outcomes especially for artemisinins, which are short-acting drugs with stage-specific activity, delaying the start of treatment until the most sensitive parasite stage occurs would be unethical. Lengthening treatment regimens to cover a full number of IDCs may be an alternative approach to improve efficacy, decrease variation and reduce treatment failure – thus curbing the evolution of drug resistance.