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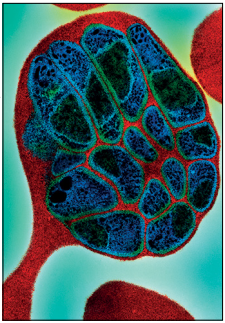
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Multidrug-resistant *Plasmodium falciparum* malaria in the Greater Mekong subregion



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Over the past decade, the burden of malaria has been greatly reduced in the Greater Mekong subregion, although artemisinin-resistant parasites have emerged,^{1,2} and high rates of treatment failure on dihydroartemisinin-piperaquine have been reported in Cambodia since 2012.³⁻⁷ Unsurprisingly, this situation is linked to the aggressive strategies implemented in this region to eliminate malaria and the inevitable massive reduction in the *Plasmodium falciparum* parasite population, leading to selection of best-adapted, multidrug-resistant parasites. In this context, identifying and circumventing survival strategies used by multidrug-resistant *P falciparum* populations is a major public health issue.⁸

In *The Lancet Infectious Diseases*, Roberto Amato and colleagues⁹ present a timely, original, and in-depth genetic analysis of the origins of *P falciparum* parasites resistant to dihydroartemisinin-piperaquine using genome sequence data of samples collected in Cambodia from 2007 to 2013. First, they confirmed the multiple origins of artemisinin-resistant parasites (24 distinct *kelch13* mutations) in western Cambodia, and then the selection of a predominant *kelch13* 580Tyr mutant over a period of 7 years. Six different origins of the 580Tyr mutant were detected, but one lineage named KEL1 largely predominated. Consistent with reports from Imwong and colleagues,^{10,11} Amato and colleagues showed that this lineage had outcompeted lineages with other 580Tyr alleles and had spread eastward through the parasite population via recombination.

Second, the authors observed a single major origin of *plasmepsin* 2-3 amplifications, indicating that piperaquine-resistant *P falciparum* parasites were probably derived from the same epidemiological origin (named the PLA1 lineage by the authors). Third, they showed that dihydroartemisinin-piperaquine resistance rapidly spread via diffusion of the KEL1/PLA1 co-lineage from western to northeastern Cambodia. Confined to western Cambodia until 2011, in 2012-13, the KEL1/PLA1 co-lineage was observed in northern Cambodia (close to the Cambodian-Laos border) in isolates sharing much higher levels of co-ancestry with western Cambodian parasites than the rest of the local

parasite population. Taken together, the results of the study suggest that antimalarial drugs exerted strong selection on the parasite genomes in this endemic area, recognised as the epicentre of emergence of multidrug resistance. The authors provided answers to pressing questions regarding the nature of parasites spreading across the Greater Mekong subregion and their susceptibility to alternative drug combinations, and discussed the major risks and uncertainties in the longer term.

The results of this study are reminiscent of the evolution of chloroquine resistance, wherein multiple *P falciparum* chloroquine resistance transporter (*Pfcr*) alleles emerged in southeast Asia before one allele (the CVIET allele) eventually spread to Africa, leading to millions of deaths. Obviously, this scenario should be avoided for artemisinin combination therapy. For chloroquine, the molecular signatures of resistance were only detected in early 2000, long after resistant parasites had spread outside their original focus. The spread of strains resistant to artemisinin combination therapy in western Cambodia is underway; however, it is reassuring to learn from this study that genomic tools are available to monitor the onset of this spread and, by contrast with chloroquine resistance, to track resistant parasites in real time.

We must take advantage of this situation. One way is to improve understanding of the causes of emergence and selection of resistance to artemisinin combination therapy by progressing analyses of parasite population genetics. For example, the early events associated with dihydroartemisinin-piperaquine resistance should be identified through analysis of samples collected before 2007. Moreover, studies could investigate additional mutations, genetic determinants, and specific genetic backgrounds conferring selective advantage to the KEL1/PLA1 co-lineage (eg, increased drug resistance, improved fitness of the asexual stages in the human host, increased transmissibility by increasing gametocyte numbers, favouring transmission to *Anopheles* spp mosquitoes). Additionally, we need to implement vigilant surveillance of drug resistance to closely follow the effect of using artesunate-mefloquine as first-line

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treatment on *P falciparum* populations in Cambodia and to track emergence of the double amplification of *pfmdr1* and *pfplasmepsin2*, already observed among 580Tyr mutants.¹² Finally, the opportunity exists to improve basic knowledge through studying parasites from areas of low endemicity where drug pressure is high but resistance to artemisinin combination therapy has not developed. This strategy would help to identify what makes parasites from western Cambodia unique regarding the emergence of antimalarial resistance.

We are confident that genomic studies will help to streamline the use of antimalarial drugs and improve local anti-malaria strategies through identification of weak points in the parasite populations.

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- 1 Arie F, Witkowski B, Amaratunga C, et al. A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria. *Nature* 2014; **505**: 50–55.

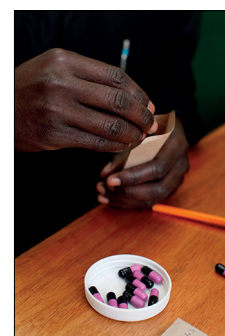
- 2 WHO. Status report on artemisinin and ACT resistance (April 2017). <http://www.who.int/malaria/publications/atoz/artemisinin-resistance-april2017/en> (accessed Jan 2, 2018).
- 3 Amato R, Lim P, Miotto O, et al. Genetic markers associated with dihydroartemisinin-piperazine failure in *Plasmodium falciparum* malaria in Cambodia: a genotype-phenotype association study. *Lancet Infect Dis* 2017; **17**: 164–73.
- 4 Duru V, Khim N, Leang R, et al. *Plasmodium falciparum* dihydroartemisinin-piperazine failures in Cambodia are associated with mutant K13 parasites presenting high survival rates in novel piperazine in vitro assays: retrospective and prospective investigations. *BMC Med* 2015; **13**: 305.
- 5 Leang R, Taylor WR, Bouth DM, et al. Evidence of *Plasmodium falciparum* malaria multidrug resistance to artemisinin and piperazine in western Cambodia: dihydroartemisinin-piperazine open-label multicenter clinical assessment. *Antimicrob Agents Chemother* 2015; **59**: 4719–26.
- 6 Witkowski B, Duru V, Khim N, et al. A surrogate marker of piperazine-resistant *Plasmodium falciparum* malaria: a phenotype-genotype association study. *Lancet Infect Dis* 2017; **17**: 174–83.
- 7 WHO. World malaria report 2017. <http://www.who.int/malaria/publications/world-malaria-report-2017/en> (accessed Jan 2, 2018).
- 8 Roberts L. Drug-resistant malaria advances in Mekong. *Science* 2017; **358**: 155–56.
- 9 Amato R, Pearson RD, Almagro-Garcia J, et al. Origins of the current outbreak of multidrug-resistant malaria in southeast Asia: a retrospective genetic study. *Lancet Infect Dis* 2018; published online Feb 1. [http://dx.doi.org/10.1016/S1473-3099\(18\)30068-9](http://dx.doi.org/10.1016/S1473-3099(18)30068-9).
- 10 Imwong M, Hien TT, Thuy-Nhien NT, Dondorp AM, White NJ. Spread of a single multidrug resistant malaria parasite lineage (*PfPailin*) to Vietnam. *Lancet Infect Dis* 2017; **17**: 1022–23.
- 11 Imwong M, Suwannasin K, Kunasol C, et al. The spread of artemisinin-resistant *Plasmodium falciparum* in the Greater Mekong subregion: a molecular epidemiology observational study. *Lancet Infect Dis* 2017; **17**: 491–97.
- 12 Rossi G, De Smet M, Khim N, Kindermans JM, Menard D. Emergence of *Plasmodium falciparum* triple mutant in Cambodia. *Lancet Infect Dis* 2017; **17**: 1233.

Time to overcome pretreatment HIV drug resistance

Antiretroviral therapy (ART) coverage among people living with HIV reached 53% worldwide in 2016, representing 21 million people on treatment.¹ As the number of people accessing ART increases, the prevalence of pretreatment drug resistance has increased in several low-income and middle-income countries (LMICs).² A recent WHO report showed that the prevalence of pretreatment resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) surpassed 10% in six of 11 countries surveyed.³ Is this a threat for the UNAIDS target of eliminating HIV as a concern for public health by 2030?

In *The Lancet Infectious Diseases*, Ravindra Gupta and colleagues⁴ present compelling results from a drug resistance epidemiology study based on the meta-regression of 358 datasets that included 56 044 adults

initiating ART across 63 countries, with or without previous ART exposure. The investigators found that the prevalence of pretreatment NNRTI resistance is rising, with a significant annual increase in the odds of pretreatment resistance of 23% in southern Africa, 17% in eastern Africa and in western and central Africa, and 11% in Asia and in Latin America and the Caribbean. By contrast, resistance to nucleoside reverse transcriptase inhibitors remained below 5% in all regions, with a significant increase only evident in southern and eastern Africa. However, available data show that pretreatment NNRTI resistance is significantly more prevalent in people with previous ART exposure. Treatment failure with an NNRTI-based regimen leads to the emergence of drug-related



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