Dihydroartemisinin-piperaquine: if it works for control, can we use it for elimination?

Historically, antimalarial drugs have been used at a population level in malaria-endemic areas with the objective of decreasing the burden, impact, and transmissibility of malaria.[1] Continuous chemoprophylaxis, once experimented but never seriously considered a feasible wide-scale implementable strategy, has been superseded by the concept of intermittent treatment targeting different population groups, presenting many advantages, including non-interference with the acquisition of natural immunity against malaria. A fundamental premise for the use of any drug as part of population wide distribution efforts, besides its efficacy, is that the drug is sufficiently safe so as to not to risk endangering the healthy individuals that will be exposed to it. The artemisinin-derived combination dihydroartemisinin-piperaquine (DP), registered under the European Medicines Agency in 2011,[2] would appear as an ideal candidate for the treatment of malaria, not only because of its high-demonstrated efficacy, but on account of its excellent tolerability and good safety profile, well reported in the literature.[3–5] From a preventive point of view, the long half-life of the partner drug piperaquine conveys protection of 22 days for adult patients and around 20 days for paediatric patients,[2] indicating a better post-treatment prophylactic effect than other combination therapies.[3,6,7] In the *Lancet Infectious Diseases*, Julie Gutman and colleagues analyse the safety, tolerability, and efficacy of repeated doses of DP, for the treatment and prevention of malaria, with a particular focus on its use as intermittent preventive treatment (IPT).[8] Their meta-analysis, looking at over 4000 patients exposed to repeated courses of DP, substantiates the high efficacy of this drug in terms of controlling malaria and all-cause hospital admission, and the good tolerability of repeated treatment schemes, with no evidence of arrhythmias secondary to the potential QT prolongation effect of cumulative doses of piperaquine after repeated doses. Although numbers are clearly insufficient to rule out this rare, life-threatening complication, and the small number of carefully ECG monitored patients calls for caution and further cardio safety studies, this analysis adds up to the growing body of evidence supporting the potential of this drug for IPT strategies. as an alternative to the currently recommended drugs. In areas where transmission remains high, it may be prudent to restrict ACTs for the treatment of cases, and not overexpose this drug family for prophylactic purposes.[9]

The authors are, however, shy to extend their recommendations for the use of DP for elimination purposes. Indeed, many of the considerations that they ponder for the use of DP as IPT in restricted population groups, including repeated dosing, apply to its wider use in mass drug administration (MDA) campaigns that target the interruption of transmission. It is precisely DP's longer-lasting post-treatment prophylactic effect that is appealing as an elimination drug, being the basis for massive use in Zambia[10] and Mozambique[11] in ambitious malaria elimination demonstration projects. In elimination settings, careful pharmacovigilance should be coupled to the assessment of the effectiveness of drug deployment, and inform on the occurrence of rarer safety events, so as to help build a more definitive case for the adequacy of the chosen drug for MDA. If transmission is successfully interrupted, legitimate concerns on the risks of fuelling drug resistance should become less pressing.

Pregnant women and very young children are often neglected in the assessment of the efficacy and safety of new drugs, or new uses of already existing drugs. For DP, this is not the case, and a robust portfolio of data has been compiled in recent years, both regarding the treatment and prevention of malaria during pregnancy[6,12] and infancy[13] including the recent development of a dispersible paediatric formulation (NCT01992900). The safety and pharmacological interactions of IPTp-SP need to be assessed in HIV-positive pregnant women already receiving antiretrovirals, understanding that in this particularly vulnerable group, the use of sulphadoxine-pyrimethamine is incompatible with cotrimoxazole prophylaxis.

Current WHO recommendations for the use of ACTS in pregnancy approach acceptance of ACT use throughout the entire pregnancy, because the risk-benefit ratio still favours the quick elimination of malaria infections

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in vulnerable pregnant populations.[9] In MDA efforts, however, use of ACTs in the first term of pregnancy should not be recommended, as the risks of exposing healthy uninfected pregnant women outweigh the potential community benefits of interrupting transmission. For this reason, adequate pregnancy detection strategies are mandatory in malaria MDA efforts using ACTs.

Debate is necessary for more proactive use of drugs to achieve the immensely ambitious goal of malaria eradication, but for the time being, DP seems to be a good candidate, both for IPT and elimination purposes.

Quique Bassat, Clara Menéndez*
ISGlobal, Barcelona Ctr Int Health Res. (CRESIB), Hospital Clínic–Universitat de Barcelona, Barcelona, Spain (QB); Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique (CM)
quique.bassat@isglobal.org

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1 Greenwood B. Anti-malarial drugs and the prevention of malaria in the population of malaria endemic areas. *Malaria J* 2010; **9** (suppl 3)**:** S2.
2 Sigma-tau Pharmaceuticals. Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001199/WC500118113.pdf (accessed Sept 28, 2016).
3 Zani B, Gathu M, Donegan S, Olliaro PL, Sinclair D. Dihydroartemisinin-piperaquine for treating uncomplicated Plasmodium falciparum malaria. *Cochrane Database Syst Rev* 2014; **1:** cd010927.
4 Keating GM. Dihydroartemisinin/Piperaquine: a review of its use in the treatment of uncomplicated *Plasmodium falciparum* malaria. *Drugs* 2012; **72:** 937–61.
5 Adjei A, Narh-Bana S, Amu A, et al. Treatment outcomes in a safety observational study of dihydroartemisinin/piperaquine (Eurartesim((R))) in the treatment of uncomplicated malaria at public health facilities in four African countries. *Malaria J* 2016; **15:** 43.
6 Pekyi D, Ampromfi AA, Tinto H, et al. Four artemisinin-based treatments in african pregnant women with malaria. *New Eng J Med 2016*; **374:** 913–27.
7 Pfeil J, Borrmann S, Bassat Q, Mulenga M, Talisuna A, Tozan Y. An economic evaluation of the posttreatment prophylactic effect of dihydroartemisinin-piperaquine versus artemether-lumefantrine for first-line treatment of plasmodium falciparum malaria across different transmission settings in Africa. *Am J Trop Med Hyg* 2015; **93:** 961–66.
8 Gutman J, Kovacs S, Dorsey G, Stergachis A, O ter Kuile F. The safety, tolerability and efficacy of repeated doses of dihydroartemisinin-piperaquine for the prevention and treatment of malaria: a systematic review and meta-analysis. *Lancet Infec Dis* 2016; published online Nov 16. http://dx.doi.org/10.1016/S1473-3099(16)30378-4.
9 Malaria Policy Advisory Committee to the WHO: conclusions and recommendations of eighth biannual meeting (September 2015). *Malaria J* 2016; **15:** 117.
10 Eisele TP, Silumbe K, Finn T, et al. Assessing the effectiveness of household-level focal mass drug administration and community-wide mass drug administration for reducing malaria parasite infection prevalence and incidence in Southern Province, Zambia: study protocol for a community randomized controlled trial. *Trials* 2015; **16:** 347.
11 Moonasar D, Maharaj R, Kunene S, et al. Towards malaria elimination in the MOSASWA (Mozambique, South Africa and Swaziland) region. *Malaria J* 2016; **15:** 419.
12 Kakuru A, Jagannathan P, Muhindo MK, et al. Dihydroartemisinin-piperaquine for the prevention of malaria in pregnancy. *N EngJ Med* 2016; **374:** 928–39.
13 Bassat Q, Mulenga M, Tinto H, et al. Dihydroartemisinin-piperaquine and artemether-lumefantrine for treating uncomplicated malaria in African children: a randomised, non-inferiority trial. *PLoS One* 2009; **4** (11)**:** e7871.