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Improving access to new tools for relapsing malaria

Placing the threat of relapse in its proper context

For a long time, *Plasmodium vivax* malaria was considered less severe than that caused by *Plasmodium falciparum*, and its clinical impact underestimated. However, this notion has changed, especially in terms of the impact on young children and pregnant women.[1] Furthermore, *P. vivax* malaria is a particular challenge for elimination efforts due to the complex life cycle of the parasite. One infectious mosquito bite can cause both a blood-stage and liver-stage parasitic infection. If untreated, the liver-stage infection can lie dormant and then reactivate causing the patient to relapse repeatedly with new bouts of malaria. Transmission of the parasite is also driven largely by relapses from dormant liver stages.

Single-dose tafenoquine (*Krintafel/Kozenis*),[2] developed by GSK and Medicines for MMV, represents a significant step forward, compared to the predominant standard of care (7-to-14-day primaquine regimens) for the treatment of the liver-stage infection to prevent *P. vivax* relapse. Expanding access to both treatments is crucial to prevent patient suffering and to eliminate the disease. However, their use in national malaria programmes remains a challenge. Even though both drugs are well tolerated by most people, in some individuals with lower levels of glucose-6-phosphate dehydrogenase (G6PD) – an enzyme that protects red blood cells from premature destruction – these drugs may cause serious haemolytic side effects. Testing for G6PD deficiency before prescribing this class of drug is therefore important for patient safety. New tools, including a quantitative, point-of-care G6PD test are becoming available and are starting to be used by several national malaria programmes.

In 2021, MMV and partner PATH, launched the Partnership for Vivax Elimination (PAVE) to accelerate the elimination of *P. vivax* malaria. Under this initiative, the first real-world study of a new *P. vivax* case management protocol with point-of-care G6PD testing before treatment with either single-dose tafenoquine or 7-day primaquine got underway in Brazil; plans are also in development to support additional real-world studies in Ethiopia, Indonesia, Papua New Guinea,[3] Peru and Thailand.

Brazil: first real-world use of optimized radical cure with G6PD testing, primaquine and tafenoquine gets underway

In September 2021, the first real-world study of a new protocol for *P. vivax* case management known as Tafenoquine Roll-out STudy (TRuST) started in Brazil. The study is a collaboration between the Brazilian Ministry of Health and MMV, and is led by the Tropical Medicine Foundation of Amazonas and the Tropical Medicine Research Center of Rondônia. The first phase of the pilot study started in nine higher and medium-level healthcare facilities in the municipalities of Porto Velho and Manaus within the Amazonia region. It is estimated that around 5% of the population living in the Amazonia region have G6PD deficiency.[4] Thus, health workers are fully trained in the new treatment algorithm and accurate use of the new tools. The first interim analysis assessed data from 600 patients attended to in these municipalities and concluded that patients were appropriately treated with the new drug tafenoquine based on the results of the G6PD test. In February 2022, the new treatment algorithm was rolled out at lower-level health facilities in these municipalities, expanding the study. The results of this study are expected by the end of 2022 and will help inform the Brazilian government's decision whether to incorporate tafenoquine and the G6PD test into the national health system for patients over 16 years of age.

1 Phyo AP *et al.* "Clinical impact of vivax malaria: A collection review" *PLoS Med* 19(1): e1003890 (2022) http://doi.org/10.1371/journal.pmed.1003890

2 Tafenoquine is marketed as *Kozenis* in Australia and *Krintafel* in the USA. Trademarks are owned by or licensed to the GSK group of companies.

3 Studies in Ethiopia, Indonesia, Papua New Guinea and Peru are supported with funding from Unitaid.

4 Dombrowski JG *et al.* "G6PD deficiency alleles in a malaria-endemic region in the Western Brazilian Amazon" *Malaria Journal* 16, 253 (2017) http://doi.org/10.1186/s12936-017-1889-6

INTERVIEW

Representatives of the **Brazilian Ministry of Health** and **Dr Dhelio Pereira**, Director of Clinical Research at the Tropical Medicine Research Center of Rondonia (CEPEM) discuss the results of Phase I of TRuST and the next steps.

What has Phase I of TRuST revealed so far?

Dhelio Pereira – Introduction of the G6PD test brought greater safety not only for the use of tafenoquine, but also for choosing the appropriate therapeutic regimen of primaquine. The few cases that resulted in haemolysis in this period were caused by inappropriate use of primaquine for patients with intermediate or low G6PD activity.

Ministry of Health – The first phase of the study indicated that in medium and higher-level units, tafenoquine was used appropriately in more than 95% of cases, although there were challenges for local health services in organizing the training of professionals and monitoring of patients who had used the drug.

What are the next steps in this study?

DP – The results of the first phase were presented to the Independent Study Oversight Committee, which advised the Ministry of Health, MMV and the researchers to expand the study to the second phase. The new tools were introduced at lower-level health facilities including those in rural areas following training on the G6PD test and new treatment algorithm. Now all malaria diagnostic sites in the municipalities of Manaus and Porto Velho offer G6PD testing and tafenoquine.

How will the evidence generated be used?

MOH – The study will provide data on the implementation of tafenoquine in these two municipalities. A second study being carried out alongside TRuST, known as QualiTRuST, will provide findings on the perception of health professionals and patients. The Ministry of Health will bring this together with an evaluation of the process made at the local level, an evaluation by specialists, a cost-effectiveness and budget-impact analysis and a pharmacovigilance assessment to form a submission to the National Commission on Health Technologies (CONITEC). CONITEC will then make an assessment as to whether to incorporate tafenoquine and the G6PD test into the national health system, or Sistema Único de Saúde (SUS), for patients over 16 years of age.

DP – The evidence generated will help us better understand the challenges of implementing tafenoquine in the public health service and its acceptance by health workers and the population, as well as evaluate the costs and logistics of material distribution and data collection in the Amazonia region. This information will also be invaluable to other countries that are looking at whether to implement the G6PD test and tafenoquine.

How can tafenoquine support the country's efforts to eliminate malaria (transmission, adherence, preventing relapse)?

MOH – The ability to treat hypnozoites and gametocytes in a single dose promotes better treatment adherence and, consequently, will help to reduce the transmission of *P. vivax* malaria. Furthermore, although there is no significant difference between the efficacy of tafenoquine and primaquine (a drug used for decades in Brazil), better adherence may also lead to a lower percentage of relapses in patients over 16 years of age with normal G6PD activity.

Is adherence to a 7-day treatment a challenge?

DP – In regions where the number of cases of *P. vivax* malaria is decreasing, knowledge about the disease also decreases and the importance of completing primaquine treatment is no longer valued, reducing adherence.

Which specific strategies are needed to improve adherence of primaquine within affected communities?

MOH – Health education actions with better targeting and accessible language for the affected populations, as well as the follow-up of treatment in locations with a lower level of transmission will be crucially important to ensure all patients understand the importance of completing the prescribed 7-day treatment regimen. To support this, we need operational capacity.

What has it been like to work with MMV on this project?

DP – I have been lucky enough to work with various teams within MMV, working on pre-clinical drug and compound development, diagnostic support, transmission blocking drug development and clinical trials, and now, on the implementation of two products, tafenoquine and the G6PD test. Everyone at MMV is a model of dedication, technical quality and love for what they do. Being in a malaria transmission region and being able to bring cutting-edge solutions to the local population in collaboration with MMV makes me proud and inspired to work harder and better.