

Driving inclusion of vulnerable populations to reduce the burden of relapsing malaria

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➤ Kellen with her children
Thaemilly and Maria
(Manaus, Brazil)

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2. Price RN *et al.* "Vivax malaria: neglected and not benign" *Am J Trop Med Hyg*. 77(6 Suppl):79-87 (2007). PMID: PMC2653940
3. Phyo AP *et al.* "Clinical impact of vivax malaria: A collection review" *PLoS Med*. 19(1): e1003890 (2022). doi: 10.1371/journal.pmed.1003890
4. Fernando D *et al.* "Cognitive performance at school entry of children living in malaria-endemic areas of Sri Lanka" *Trans R Soc Trop Med Hyg*. 97(2):161-5 (2003). doi: 10.1016/s0035-9203(03)90107-6
5. Vorasan N *et al.* "Long-term impact of childhood malaria infection on school performance among school children in a malaria endemic area along the Thai-Myanmar border" *Malar J*. 14:401 (2015). doi: 10.1186/s12936-015-0917-7
6. Brasill LMBF *et al.* "Cognitive performance of children living in endemic areas for *Plasmodium vivax*" *Malar J*. 16(1):370 (2017). doi: 10.1186/s12936-017-2026-2
7. See Chapter 5.
8. Tafenoquine is approved for patients at least 16 years old in Australia, Brazil, Colombia, Peru, Thailand, and the USA, with additional submissions pending review in endemic countries. Approvals in Colombia and the Philippines were obtained in 2022. It is marketed as *Krintafel* in the USA; trademarks are owned or licensed by the GSK group of companies.
9. The label for tafenoquine restricts its use to patients with at least 70% G6PD activity; however, primaquine can be given to people with at least 30% G6PD activity.
10. See www.path.org.
11. The test is approved in countries including Cambodia, Djibouti, India, Indonesia, Myanmar, Pakistan, the Philippines, Saudi Arabia and Thailand.

Simplifying radical cure for *Plasmodium vivax*

The malaria parasite *Plasmodium falciparum*, which dominates in Africa, is responsible for the majority of malaria deaths worldwide. The parasite *Plasmodium vivax*, responsible for relapsing malaria, dominates in Central and South America, South and South-East Asia and the Horn of Africa, where it presents a different set of challenges. In these regions, often-neglected populations such as migrant workers, displaced people and indigenous communities are disproportionately affected.

Unlike *P. falciparum*, *P. vivax* can cause both a blood-stage infection (causing an acute malaria episode) and a liver-stage infection, which can lie dormant and then reactivate if not treated, causing relapses that may occur weeks or months after the initial infection. This makes *P. vivax* a particular challenge for elimination efforts, with transmission driven largely by relapses from dormant liver stages.¹

For many years, *P. vivax* malaria was considered relatively benign. However, evidence has emerged that it can also lead to severe disease and death,² with young children and pregnant women at highest clinical risk.³ Children are especially vulnerable to cumulative anaemia from repeated relapses, and to chronically swollen spleens (splenomegaly), which may rupture and cause internal haemorrhaging. Moreover, children experiencing repeated infections are likely to suffer physical and cognitive impairment,^{4,5,6} with adverse consequences for their development and education. *P. vivax* malaria in pregnancy is also a major cause of morbidity and mortality, with potential consequences like those of *P. falciparum* disease.⁷

Achieving 'radical cure' for *P. vivax* involves treating both the blood stage and the liver stage of infection. The current standard of care involves 3 days of chloroquine or an artemisinin-based combination treatment (ACT) to treat the blood stage and either 7 or 14 days of primaquine for the liver stage. Adherence to the primaquine regimen is problematic, as symptoms improve rapidly once the blood-stage infection is cleared. In addition to the obvious risk to patients, poor adherence fuels transmission, as dormant liver-stage parasites become a reservoir for infection.

Tafenoquine (*Krintafel/kozenis*),⁸ developed in partnership between GSK and MMV with the support of endemic-country partners, represents a significant advance in treatment of liver-stage infection because of its single-dose administration, which eliminates the problem of poor adherence.

Both tafenoquine and primaquine are generally well tolerated but can cause severe haemolytic anaemia (destruction of red blood cells) in people deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD).⁹ Testing for G6PD deficiency is therefore important for patient safety, but has previously presented a logistical challenge for National Malaria Control Programmes (NMCPs).

A quantitative point-of-care G6PD diagnostic test has been developed by SD Biosensor with support from the global non-profit organization PATH.¹⁰ The portable, battery-operated device can distinguish deficient, intermediate and normal levels of G6PD enzyme activity which is essential for the prescription of tafenoquine. The test received regulatory approval from the Australian Therapeutic Goods Administration (TGA) in 2021, certifying that it is appropriate for use in point-of-care settings and meets rigorous quality standards.¹¹

An implementation study assessing the feasibility of providing tafenoquine or primaquine based on G6PD test results at different levels of the health system was completed in 2022 in Brazil (the TRuST study),¹² and a second was started

in Thailand in May 2022 (the ARCTIC study).¹³ In 2023, additional studies are planned in Ethiopia and Peru with tafenoquine, as well as in Indonesia and Papua New Guinea where only primaquine will be used.¹⁴

Approval of novel paediatric relapse-prevention treatment

In March 2022, the Australian TGA approved use of single-dose tafenoquine in combination with chloroquine for radical cure of *P. vivax* malaria in children at least 2 years old. A child-friendly dispersible formulation was developed in a partnership between GSK and MMV. The submission was supported by a Phase IIb study¹⁵ evaluating tafenoquine dosages based on weight for children aged from 2 to 15 years and weighing ≥ 10 kg, which showed pharmacokinetics,¹⁶ safety and efficacy similar to those previously observed.

Moreover, 95% of the 60 participants showed no recurrence of *P. vivax* malaria over 4 months of follow-up.¹⁷

TGA approval is supporting registrations in endemic countries where tafenoquine could contribute to malaria elimination goals. Tafenoquine for paediatric use represents a step towards addressing the needs of children in these countries, who are particularly vulnerable to repeated *P. vivax* episodes.

Brazil: Tafenoquine Roll-out Study (TRuST) updates

The Brazilian Amazon region accounts for 99% of malaria cases in the country. The disease has considerable economic and social impact, perpetuating cycles of poverty.¹⁸

One of the main challenges to malaria control in Brazil is the difficulty of accessing remote populations, notably indigenous communities. Adherence to treatment is another major challenge, as failure to complete treatment leads to relapses and continued transmission.

The first real-world study of tafenoquine and quantitative point-of-care G6PD testing, known as TRuST, was launched in Brazil in September 2021. The study, a collaboration between the Brazilian Ministry of Health (MoH) and MMV, was led by malaria experts from the Dr Heitor Vieira Dourado Tropical Medicine Foundation (*Fundação de Medicina Tropical Doutor Heitor Vieira Dourado*; FMT-HVD) and the Tropical Medicine Research Centre (*Centro de Pesquisa em Medicina Tropical*; CEPeM).¹⁹

TRuST assessed the feasibility of providing appropriate relapse-prevention treatment with tafenoquine or primaquine based on G6PD test results. Within the framework of TRuST, a qualitative study known as QualiTRuST was conducted by

FMT-HVD to assess the understanding and acceptability of the new tools amongst health workers and patients.

The first phase was conducted in nine higher- and medium-level health facilities (hospitals) in Porto Velho and Manaus, in the Amazon region.²⁰ In February 2022, the study was expanded to 40 lower-level facilities in the same municipalities. Enrolment finished in August 2022, and in November the second interim analysis showed that more than 99% of patients treated with tafenoquine had been treated appropriately based on quantitative G6PD test results.

In December 2022, the MoH submitted a dossier on tafenoquine and quantitative G6PD testing to the National Committee for [health] Technology Incorporation (CONITEC²¹). This dossier, based on consolidated results from the TRuST first and second interim analyses, QualiTRuST, a cost-effectiveness analysis and a budget impact analysis, will inform the decision on the incorporation of tafenoquine and quantitative G6PD testing into the Brazilian health system for patients at least 16 years old.

Analysis of full safety and efficacy data is ongoing, with a report expected in March 2023 and publications thereafter.

12. Tafenoquine Roll-out Study. See also the video "From science to real life: Tackling relapsing malaria in the Amazon":



13. Assessing Radical Cure Treatment in routine Care. See also the video "The ARCTIC study: optimizing *P. vivax* radical cure in Thailand":



14. These additional studies are supported by funding from Unitaid.

15. TEACH – Tafenoquine Exposure Assessment in Children.

16. Characteristics describing how a drug is absorbed, distributed, metabolized and excreted from the body.

17. Vélez ID *et al.* "Tafenoquine exposure assessment, safety, and relapse prevention efficacy in children with *Plasmodium vivax* malaria: open-label, single-arm, non-comparative, multicentre, pharmacokinetic bridging, phase 2 trial" *Lancet Child Adolesc Health*. 6(2):86-95 (2022), doi: 10.1016/S2352-4642(21)00328-X

18. Adults may be too ill to work or carry out family responsibilities, or may lose jobs after multiple absences; children may be unable to attend school or suffer from cognitive problems.

19. In Amazonas and Rondônia, respectively.

20. An estimated 5% of the population in this region is G6PD-deficient. (Dombrowski JG *et al.* "G6PD deficiency alleles in a malaria-endemic region in the Western Brazilian Amazon" *Malar J*. 16(1):253 (2017), doi: 10.1186/s12936-017-1889-6

21. National Committee for [health] Technology Incorporation (Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde – CONITEC).



← A woman holds her Cartão Malaria and primaquine prescription (Manaus, Brazil)



Revisiting Raquel: Single-dose tafenoquine for *P. vivax* malaria

Raquel da Silva, shown here with her son Camilinho, has lived in Manaus in Brazil's Amazonas State since her childhood. Today she shares her home on the banks of the Rio Negro with her husband Camilo, their three children, her mother-in-law and her grandmother-in-law. On the weekends, she works in a restaurant.

As a mother of three, Raquel needs her energy to keep up with her children, but living in one of the most malaria-affected areas in the country she has been ill with the disease many times. She has lost track of how many times she has contracted malaria but estimates it must be at least a dozen. In 2022 alone, she got sick with malaria at least three times: twice with *Plasmodium falciparum* malaria and once with *P. vivax* malaria, which is more common in Latin America.

The first time MMV met Raquel in 2020, she was unwell. At the time, *P. vivax* malaria required a full 7-day treatment to cure and prevent relapse, and since she had a 6-month-old baby at home and her husband was away working, she felt unable to complete the full treatment course. **"I took just enough so my symptoms would improve."** She dealt with many bouts of the illness, accompanied by low energy, chills and fever.

In 2022, however, things were different. When she got malaria, she received a new drug: tafenoquine. Developed in partnership between GSK and MMV,

this drug is a single-dose radical cure for *P. vivax* malaria, meaning that it prevents relapse when accompanied by chloroquine, an antimalarial drug already widely distributed and used in Brazil's health system.

Manaus, where Raquel lives, and Porto Velho are the only cities in Brazil authorized by the Brazilian Ministry of Health to prescribe tafenoquine after quantitative point-of-care G6PD testing as part of a temporary implementation plan in the national public health system. This implementation is accompanied by the MoH and MMV-co-sponsored Tafenoquine Roll-out Study (TRuST), described above.

For patients with normal G6PD enzyme activity, the new treatment protocol with tafenoquine is much simpler, something that makes a big difference in the lives of patients like Raquel.

Raquel is optimistic about the new possibilities that the drug provides. She says that, although she also takes preventive measures such as using bed nets, the drug provides a sense of security in case she or her family members do fall ill again.

Story

Tackling relapsing malaria in Thailand

In the Mekong region of Southeast Asia, as NMCPs have substantially reduced the incidence of *P. falciparum* malaria, *P. vivax* malaria has become more dominant and is threatening elimination targets due to the challenges of effective radical cure.

In Thailand, people living in forested border areas are the main population at risk of *P. vivax* malaria, as transmission is associated with two vectors found in these settings.²² This population includes migrant workers, whose occupations²³ increase their risk of contact with infectious mosquitoes, as well as people displaced by conflict and economic hardship who are at risk due to poor healthcare access. Conflict and economic disruption can also undermine malaria control efforts, and migration can re-establish the parasite where it has been previously eliminated. These populations – and *P. vivax* patients in general – face substantial challenges to adherence to the 14-day primaquine regimen, which single-dose tafenoquine could potentially overcome.

In May 2022, the Thai Ministry of Public Health's Division of Vector-Borne Diseases, with the support of MMV, enrolled the first patients in the ARCTIC study. This feasibility study, similar to TRuST, is investigating real-world use of quantitative point-of-care G6PD testing to determine appropriate relapse-prevention treatment with tafenoquine or primaquine. This is the first such study with tafenoquine in the Asia-Pacific region and should provide evidence of its potential role in achieving Thailand's 2024 malaria elimination goal.

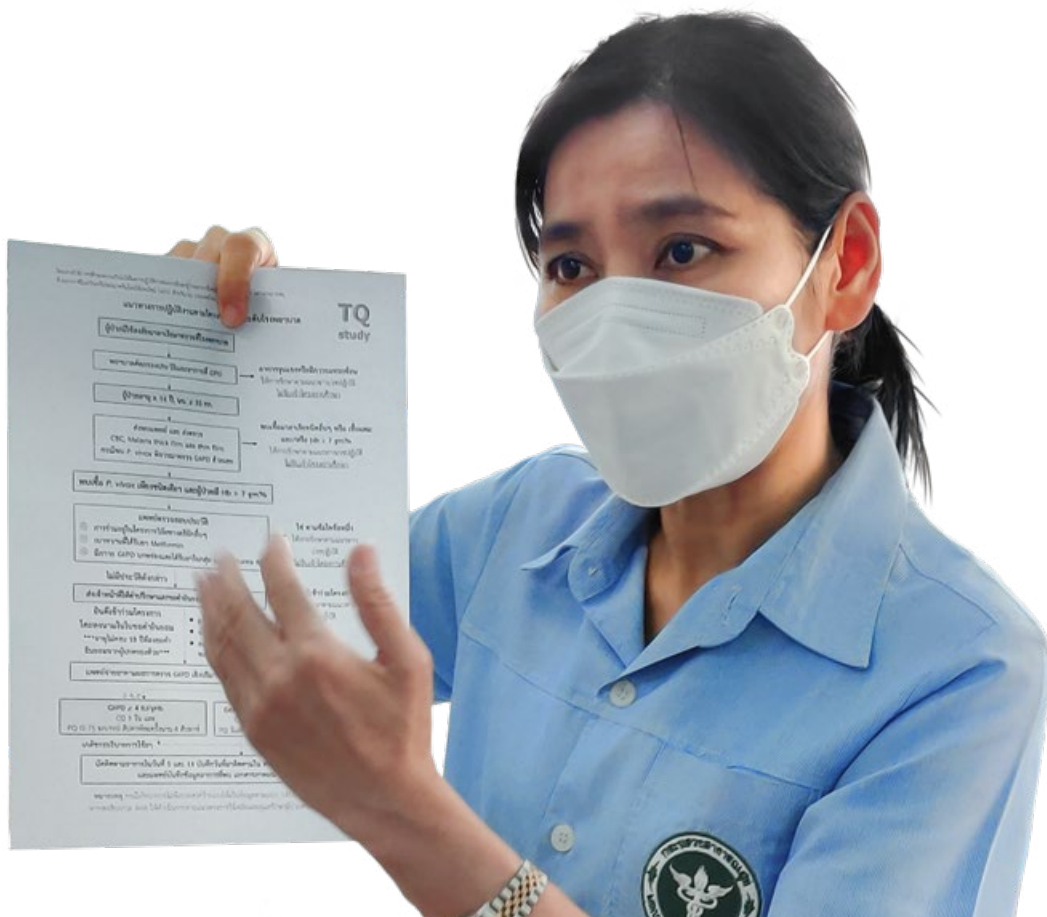
ARCTIC is being conducted in Mae Hong Son and Yala provinces, where quantitative G6PD testing has been available in district hospitals since 2020.²⁴ Mae Hong Son province, near the Thai-Myanmar border, has experienced a significant rise in malaria cases with the increase in refugees crossing the border.

In November 2022, an interim analysis showed that all of the first 50 patients had received appropriate treatment (tafenoquine or primaquine) based on G6PD test results. An independent study oversight committee approved expansion from high-level health facilities (hospitals) to lower-level malaria clinics in December 2022. Enrolment is expected to continue until June 2023. ●



We are thrilled to be working hand in hand with the Thai Ministry of Public Health on the ARCTIC study, assessing whether tafenoquine can be integrated into routine care in Thailand. Single-dose tafenoquine has great potential to reduce the burden of *P. vivax* by increasing treatment adherence, taking us one step closer to eliminating this particularly challenging species.”

— Dr Elodie Jambert, Senior Director, Access & Product Management, MMV



22. Specifically, *Anopheles dirus* and *An. minimus*. See “Thailand, LAO PDR and Regional Malaria Operational Plan FY 2018”, President’s Malaria Initiative, USAID (2018), p. 6: <https://reliefweb.int/report/thailand/presidents-malaria-initiative-thailand-malaria-operational-plan-fy-2018>

23. Notably mining, forestry and agriculture.

24. Prevalence of G6PD deficiency ranges from 3% to about 18% in Thailand, varying with region and ethnic group.

A Thai MoH representative presents the ARCTIC study to Mae Hong Son hospital staff