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Plasmodium vivax tool brief: radical cure treatments

Overview

Plasmodium vivax (P. vivax) is the most dominant malaria species globally after *Plasmodium falciparum*, with 6.9 million cases reported in 2022.[1] Prevalent in most tropical and sub-tropical areas in the world, *P. vivax* is associated with recurring disease and death in severe cases with children aged 5 years or less, pregnant women, and migrant populations at particular risk. The complex lifecycle of *P. vivax* includes a blood stage and an undetectable dormant liver stage called the hypnozoite, which can reactivate, causing multiple episodes of malaria from a single infectious bite. Moreover, *P. vivax* parasites are transmissible prior to patients becoming symptomatic, which complicates efforts to reduce transmission.

Known as radical cure, the treatment of *P. vivax* requires the administration of a blood and liver stage treatment to clear all parasites and prevent relapse. The acute blood-stage infection requires a schizonticide (chloroquine or artemisinin-based combination therapy [ACT]). Hypnozoites in the liver are treated with an 8-aminoquinoline (primaquine or tafenoquine) to prevent relapses. The three main barriers to *P. vivax* radical cure are:

- Adherence to full regimens (the currently recommended treatment for *P. vivax* requires a 7- or 14-day primaquine regimen in most cases or weekly treatment over 8 weeks for certain patients).
- Restrictions on liver stage treatments for particularly vulnerable groups, including pregnant and breastfeeding women and infants aged 6 months or less.
- Restrictions on liver stage treatments for individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as this class of drugs can cause dose-dependent hemolysis.

However, the recent expansion of the antimalarial toolbox and advances in the availability of point-of-care quantitative G6PD testing are making appropriate radical cure more accessible to patients, which is critical to improving patient care, reducing transmission, and supporting national malaria programs in achieving their malaria elimination goals.

Treatment overview

Radical cure requires the administration of a combination therapy (blood stage treatment in combination with liver stage treatment) to clear all parasites.

Blood-stage treatment

In areas with chloroquine-susceptible infections, uncomplicated *P. vivax* malaria is treated with blood stage schizonticides: either chloroquine or an ACT.[2] In areas with chloroquine-resistance, adults and children with uncomplicated *P. vivax* malaria should be treated with an ACT. For details of treating women during pregnancy and women who are breastfeeding please refer to the WHO Guidelines for malaria.[2]

Liver-stage treatment: 8-aminoquinolines

An 8-aminoquinoline, either primaquine or tafenoquine, is required to clear hypnozoites in the liver. Primaquine was the only option for *P. vivax* liver-stage treatment until 2018, when single-dose tafenoquine, another 8-aminoquinoline with a long half-life, first received United States (US) Food and Drug Administration and Australian Therapeutic Goods Association (TGA) approval.[3,4] Single-dose tafenoquine is a breakthrough treatment option that facilitates adherence. Primaquine is suitable for use with all blood-stage treatments, whereas tafenoquine is restricted for use only with chloroquine. For details of treating women during pregnancy and women who are breastfeeding please refer to the WHO Guidelines for malaria.

Risk of hemolysis for G6PD normal, G6PD intermediate, and G6PD deficient patients

Radical cure of *P. vivax* malaria with 8-aminoquinolines is complicated due to the risk of hemolysis in individuals with G6PD deficiency, the most common human genetic enzymatic disorder observed in many malaria-endemic countries. Most patients are unaware of their G6PD status, as clinical manifestations of G6PD deficiency are rarely demonstrated in the absence of exposure to 8-aminoquinoline drugs or other oxidant agents such as fava beans. According to the World Health Organization (WHO), patients' G6PD status should guide the administration of primaquine for preventing relapse. For tafenoquine, G6PD testing with a quantitative G6PD test is mandatory to ensure that it is only given to individuals with greater than 70% enzyme activity (G6PD normal).

- Until recently, quantitative G6PD testing could only be performed in clinical laboratories, restricting patient access in most malaria-endemic areas.[5] Now, G6PD deficiency can be screened at points of care using quantitative tests.
- Qualitative testing can determine whether an individual has normal or deficient G6PD activity levels—where activity less than 30% of normal is considered G6PD deficient. However, these tests are limited in their ability to produce robust results and cannot identify women with intermediate G6PD activity (between 30% and 70%) who are at risk of dose-dependent hemolysis. There are currently no qualitative tests with a Stringent Regulatory Approval (SRA) nor approved by WHO prequalification.
- Quantitative point-of-care testing can differentiate between deficient, intermediate, and normal G6PD enzyme activities, thereby reducing the risk of clinically significant hemolysis and can be used to determine G6PD enzymatic activity level greater than 70% (considered G6PD normal), which is a requirement per the tafenoquine label.
- The STANDARD G6PD point-of-care quantitative test by SD Biosensor is the only point-of-care test to have received SRA approval by the Australian TGA (2021) and is currently approved by the Global Fund's Expert Review Panel for Diagnostics. The Expert Review Panel for Diagnostics approval, which allows for the procurement of the STANDARD G6PD test with Global Fund and Unitaid funds, is reviewed annually. The test has also been submitted for WHO prequalification.
- For more detailed information on available tests please refer to the '*Plasmodium vivax* tool brief: Point-of-care G6PD diagnostics' developed by Partnership for Vivax Elimination (PAVE) project.

Relapse patterns: short and long latency

- Understanding relapse patterns in different regions can help inform *P. vivax* malaria control and elimination strategies.[6]

Long latency

- Temperate and sub-tropical strains have a long latency period between the primary infection and relapse, typically 8–10 months.

Short latency

- Tropical strains have short incubation times and short relapse intervals. Short-latency relapses with repeated gametocyte generation increase the probability of human-to-mosquito transmission. In contrast to the long-latency relapses for *P. vivax* malaria, relapses with short-latency infections—like the Chesson strain—occur earlier and at higher rates, with relapse rates as high as 90% within 6 weeks of the treated primary infection. Short latency strains are also considered to be more resistant to 8-aminoquinoline drugs and for primaquine it has been shown that higher doses are required.[7]

Primaquine

Primaquine was developed in 1945 and was introduced as a therapeutic intervention in the early 1950s due to its better safety profile and therapeutic ratio compared to other 8-aminoquinolines (pamaquine or pentaquine). There are no patents on primaquine. Recommended by WHO for *P. vivax* relapse prevention, primaquine kills the latent persistent stages (hypnozoites) of *P. vivax* in the liver.[8] It is also active against the asexual and sexual stages (gametocidal activity) of the parasite, reducing transmissibility.

Restrictions on use and safety considerations

As an 8-aminoquinoline, primaquine carries the risk of acute hemolytic anemia in G6PD-deficient patients. According to WHO recommendations, primaquine should not be given to pregnant women, infants aged 6 months or less, women who are breastfeeding an infant aged 6 months or less or women breastfeeding older infants who are G6PD deficient (or where the G6PD status is unknown[2]).

Adult and pediatric treatment options

There are currently three companies manufacturing and marketing primaquine. There are two SRA primaquine products included on the Global Fund list of approved malaria pharmaceutical products[9]; and a further product prequalified by WHO[a]:

- 7.5 mg film-coated tablets (marketed by Remedica Ltd).
- 15 mg tablets (marketed by Sanofi-Aventis US LLC).
- 15 mg film-coated tablets (marketed by Macleods Pharmaceuticals Ltd).
- There is currently no quality-approved pediatric formulation of primaquine included in the Global Fund list of approved malaria pharmaceutical products, and dosing for young children weighing less than 10

[a] WHO Prequalification Unit added the following primaquine product to its prequalified list: Primaquine Tablet, Film-coated 15mg - Macleods Pharmaceuticals Ltd – INDIA, https://extranet.who.int/prequal/news/first-primaquine-prequalified

kg is limited by the currently available tablet size.[b] Cutting or splitting a film-coated tablet is not recommended. Primaquine has a bitter taste which leads to low acceptability and adherence in children.

- Medicines for Malaria Venture (MMV) is currently working with Fosun Pharma to support the development of 2.5 mg and 5 mg dispersible formulations to address the unmet need for pediatric primaquine formulations.
- The Developing Paediatric Primaquine project is working with Ipca Laboratories to develop an expanded range of quality-assured, taste-masked tablet strengths: 2.5 mg; 3.75 mg and scored tablets 5 mg; 7.5 mg and 15 mg.[c]

Dosing schedules

WHO recommends using the G6PD status of patients to guide administration of primaquine.[2]

- As of 2022, WHO guidelines for malaria strongly recommend a short-course 7-day regimen of primaquine (0.5 mg/kg/day; total dose 3.5 mg/kg) for children and adults with no G6PD deficiency, aimed at improving patient adherence compared to a 14-day treatment course.[2]
- This builds on WHO's 2015 recommendation of a 14-day lower daily dose of primaquine (0.25 mg/kg/day; total dose 3.5 mg/kg) for children and adults in all transmission settings with no G6PD deficiency. The 2015 recommendation remains a treatment option.
- In 2015, WHO also recommended a higher-dose 14-day treatment course (0.5 mg/kg/day: total dose of 7 mg/kg) for frequent relapsing *P. vivax* predominant in East Asia and Oceania.
- For G6PD deficient patients, WHO recommends the use of primaquine once a week for 8 weeks (0.75 mg/kg/week: total dose of 6 mg/kg), with close medical supervision for potential primaquine-induced hemolysis. In the absence of evidence to recommend alternatives, this is considered the safest regimen for people with mild-to-moderate G6PD deficiency.
- In 2022, WHO issued a conditional recommendation against a 7-day high-daily dose primaquine treatment (1 mg/kg/day; total dose of 7 mg/kg), citing a significant increased risk of serious adverse effects.

Patient adherence considerations

Though primaquine has been the main treatment for relapsing *P. vivax* malaria for the past 70 years, its prolonged administration for 7 or 14 days is challenging, with many patients failing to complete the recommended treatment regimen unless directly observed. If patients do not complete their treatment course, they are underdosed and may therefore suffer malaria relapses. This explains why real-world efficacy (effectiveness) of primaquine is often lower than the efficacy observed under clinical trial conditions, where patients are supervised to complete the full treatment course.

Efficacy (dose-dependent safety and efficacy considerations)

Following the 2022 WHO conditional recommendation against the use of a 7-day, high-daily dose of primaquine (1 mg/kg/day), a meta-analysis was published finding the risk of *P. vivax* recurrence was

[b] The PAHO Strategic Fund Product List contains a 5 mg tablet, that is available for procurement in the region, https://www.paho.org/sites/default/files/strategic-fund-product-list-240125_0.pdf
[c] https://dpp-project.org/

significantly lower in patients treated with a high total dose of primaquine (7 mg/kg) compared to those treated with a lower total dose (approximately 3.5 mg/kg) of primaquine or untreated patients.[10] The meta-analysis suggests that high-dose primaquine has greater efficacy than low-dose primaquine in regions with both high and low relapse frequency, and that a total dose of primaquine of 7 mg/kg could reduce *P. vivax* recurrences by more than 50% in most endemic regions, with a small associated increase in gastrointestinal symptoms.

Another 2023 meta-analysis examined the relationship between varying daily doses of primaquine and the risk of hemolysis.[11] The review suggested that patients with intermediate or normal G6PD activity who received a daily dose of primaquine ranging from 0.25 mg/kg/day to 0.5 mg/kg/day demonstrated a similar risk of hemolysis compared to patients not exposed to primaquine. Likewise, treatment of patients with normal G6PD activity with doses of 0.25-1 mg/kg/day regimens were not associated with increased hemolysis risk, further supporting the safety profile of primaquine radical cure at these doses in G6PD normal patients. It is important to note however, that two female patients with intermediate G6PD activity who were treated with a 1 mg/kg/day dose did have a hemoglobin reduction of more than 25% to a concentration of less than 7 g/dL.[11]

Single-dose tafenoquine

Like primaquine, tafenoquine comes from the 8-aminoquinoline class of drugs. It was developed in partnership between GSK and MMV for the prevention of *P. vivax* relapse and first received marketing authorization approval in 2018. GSK is the drug's marketing authorization holder and the drug is marketed under the trade names Krintafel™ (for the US market) and Kozenis™ (for Australia and malaria-endemic countries). There are no patents on tafenoquine. Due to its long half-life, tafenoquine is given as a single-dose treatment, eliminating the risk of non-compliance, and resulting in high real-world efficacy.

Restrictions on use and safety considerations

Tafenoquine cannot be given to infants, pregnant women, and women who are breastfeeding infants whose G6PD status is unknown or who are G6PD deficient. Like primaquine, tafenoquine carries the risk of acute hemolytic anemia in G6PD-deficient patients. Thus, G6PD testing with a quantitative G6PD test is mandatory to ensure that it is only given to individuals with enzyme activity that is greater than 70%. Tafenoquine is also not approved for use in children aged 2 years or less.

The efficacy and safety study of tafenoquine co-administered with dihydroartemisinin-piperaquine (DHA-PQP) for the radical cure of *plasmodium vivax* malaria (INSPECTOR) conducted in Papua, Indonesia tested the superiority of DHA-PQP plus tafenoquine against DHA-PQP alone in the prevention of *P. vivax* malaria relapse at 6 months.[12] The study showed no clinically meaningful reduction in recurrence over 6 months when tafenoquine was used with DHA-PQP in comparison to DHA-PQP alone. Following these results, all tafenoquine labels were updated or directly submitted, restricting tafenoquine's use only in combination with chloroquine for the acute blood-stage infection.

Adult and pediatric treatment options

Currently tafenoquine is marketed for relapse-prevention treatment solely by GSK.

- Both the US Food and Drug Administration and Australian TGA approved the adult formulation of tafenoquine in 2018, and in 2022 the TGA expanded the approval to include the use of tafenoquine in children aged 2 years or older, including a specific dispersible pediatric formulation for children between 10 and 35 kg.

- The approval of pediatric tafenoquine by the Australian TGA in 2022 for children aged 2 years or older was supported by a pharmacokinetic bridging phase 2b clinical study, Tafenoquine Exposure Assessment in Children (TEACH), which evaluated dosages of tafenoquine based on weight for children between the age of 2 (weighing at least 10 kg) and up 15 years.[13]
- As of January 2024, tafenoquine for adults is approved in Australia, Brazil, Colombia, Ethiopia, Peru, Thailand, the Philippines, and the USA with approval pending in Myanmar, Pakistan, and Vietnam. Pediatric tafenoquine has gained approval in Australia and Brazil, and has been submitted for review in Colombia, Peru, and Thailand.[14]

Dosing schedules

Tafenoquine is administered using one of three single-dose regimens. There are currently no WHO guidelines for tafenoquine, although WHO's Malaria Policy Advisory Group has communicated that a first recommendation is expected in May 2024.[15]

- 2 x 150 mg tablets taken once in combination with chloroquine for radical cure in adolescents and adults aged 16 years or older and weighing more than 35 kg.
- 4 x 50 mg dispersible tablets taken once in combination with chloroquine for radical cure in children aged 2 years or older and weighing between 20-35 kg.
- 2 x 50 mg dispersible tablets taken once in combination with chloroquine for radical cure in children aged 2 years or older and weighing between 10-20 kg.

Efficacy

The optimum 8-aminoquinoline dose lies between the treatment benefits and treatment-related risks (mainly attributed to the subgroup of patients with G6PD deficiency), of that dose. During the clinical development program for tafenoquine, a single 300 mg dose of tafenoquine for radical cure prevented recurrence of *P. vivax* malaria over a 6-month period in 62% to 89% of cases.[16] In general, the efficacy profile of tafenoquine is similar to that of primaquine, although some geographic variability has been detected. Tafenoquine is a slowly absorbed 8-aminoquinoline antimalarial drug reaching peak plasma concentrations in 8–12 hours, (primaquine reaches peak blood plasma concentrations within four hours) and has a half-life of around 15 days (compared with 5 hours for primaquine).

Research pathways for primaquine and tafenoquine

Ongoing dose optimization research for primaquine and tafenoquine

- The Effectiveness of Novel Approaches to Radical Cure With Tafenoquine and Primaquine—a randomized controlled trial (EFFORT), is comparing the safety, effectiveness, and cost-effectiveness of novel radical cure options including single-dose tafenoquine and high- and lower-dose primaquine regimens.[17] Patient recruitment started in April 2021. There are six trial sites located across Cambodia, Ethiopia, Indonesia, and Pakistan.
- The Southeast Asia Dose Optimization of Tafenoquine (SEADOT) study aims to determine whether a 50% increase in tafenoquine dose provides better efficacy than the currently recommended 300 mg tafenoquine dose, as measured by the absence of recurrent *P. vivax* infection by 4 months.[18] This phase 4 study is expected to start in 2024 and aims to recruit patients from Cambodia, Laos, Thailand, and Vietnam.

- The Revised Tafenoquine Dose to Improve Radical Cure for Vivax Malaria (TADORE) study will evaluate efficacy, tolerability, and safety of a weight-based tafenoquine dose regimen.[19] The study aims to recruit patients from Brazil, Ethiopia, Indonesia, and Papua New Guinea and is planned to start in 2024; it will also evaluate the feasibility and acceptability of a weight-based tafenoquine dosing scheme.

Real-world feasibility and cost-effectiveness studies

- The Tafenoquine Roll-out STudy (TRuST) assessed the feasibility of providing appropriate radical cure (primaquine or tafenoquine in combination with chloroquine) based on the results of quantitative G6PD point-of-care testing, in real-world settings in two Brazilian municipalities: Manaus and Porto Velho.[20] More than 6,000 patients were recruited between September 2021 and August 2022. The results from the study revealed the following:
    - The level of compliance with the new treatment protocol of providing tafenoquine based on appropriate levels of G6PD activity was more than 99% and consistent across higher/medium- and lower-level health care facilities.
    - Routine testing for G6PD activity before providing radical cure was feasible at different levels of the Brazilian health system.
    - As with any new intervention, there was a steep learning curve for health care providers to incorporate G6PD testing into their routine at health units. The challenges experienced when first using the quantitative G6PD test were overcome with training and practice.
- A cost effectiveness analysis of tafenoquine following G6PD screening versus primaquine for treatment of *P. vivax* malaria in Brazil used transmission modeling to consider four different treatment scenarios.[21] In each of the scenarios, the study demonstrated that tafenoquine prescribed after G6PD testing with the STANDARD G6PD test was highly likely to be cost-effective in Brazil.
- The Thai Ministry of Health and MMV recently conducted a feasibility study known as ARCTIC (Assessing Radical Cure Treatment in routine Care) in Thailand, looking at providing primaquine or tafenoquine after quantitative G6PD testing.[22] The results of this study have been analyzed and are planned to be published in 2024.
- Unitaid-supported operational research studies are currently examining the feasibility, acceptability, and cost implications of providing tafenoquine or high-dose primaquine over 7 days after quantitative G6PD testing in real-world settings in five countries (Ethiopia, Peru, and Vietnam for tafenoquine; Indonesia and Papua New Guinea for high-dose primaquine).[23,24] The studies in Indonesia, Papua New Guinea, and Peru got underway in 2023. The studies in Ethiopia and Vietnam are planned to start in 2024.

For the latest planned and ongoing clinical trials and feasibility studies involving tafenoquine, consult the *P. vivax* malaria study database.[25]

Annex 1: Treatment Options for malaria: Preventing relapse in *P. vivax*

Regimens	G6PD status	Duration	Daily/total dose	WHO guidelines (2023)
Primaquine regimens				
Short-course standard dose treatment to prevent relapse 'lower dose' (children and adults with no G6PD deficiency in all transmission settings)	G6PD normal	7 days	Daily: 0.5 mg/kg/day Total: 3.5 mg/kg	Strong recommendation **for**, very low certainty evidence
Short-course standard high-dose treatment to prevent relapse	G6PD normal	7 days	Daily: 1.0 mg/kg/day Total: 7 mg/kg	Conditional recommendation **against**, very low certainty evidence
Preventing relapse in children and adults with no G6PD deficiency in all transmission settings	G6PD normal and intermediate	14 days	Daily: 0.25 mg/kg/day Total: 3.5 mg/kg	Strong recommendation **for**, high certainty evidence
For tropical, frequent-relapsing predominant in East Asia and Oceania	G6PD normal	14 days	Daily: 0.5 mg/kg/day Total: 7 mg/kg	Strong recommendation **for**, high certainty evidence
Preventing relapse in people with G6PD deficiency (with close medical supervision for potential primaquine-induced hemolysis)	G6PD deficient	8 weeks	Daily: 0.75 mg/kg/day Total: 6 mg/kg	Conditional recommendation **for**, very low certainty evidence
Tafenoquine regimens				
Preventing relapse in adolescents and adults aged 16 years or older and weighing more than 35 kg	G6PD normal only	1 day	2 x 150 mg tablets taken once (total 300 mg)	No WHO guideline for tafenoquine at present
Preventing relapse in children aged 2 years or older and weighing between 20-35 kg	G6PD normal only	1 day	4 x 50 mg dispersible tablets once (total 200 mg)	No WHO guideline for tafenoquine at present
Preventing relapse in children aged 2 years or older and weighing between 10-20 kg	G6PD normal only	1 day	2 x 50 mg dispersible tablets once (total: 100 mg)	No WHO guideline for tafenoquine at present

Abbreviations: G6PD, glucose-6-phosphate dehydrogenase; WHO, World Health Organization

Annex 2: Key published studies on primaquine and tafenoquine

Tafenoquine

1. Hemolytic Potential of Tafenoquine in Female Volunteers Heterozygous for Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency (G6PD Mahidol Variant) versus G6PD-Normal Volunteers (2017): https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5590573/
2. Single-Dose Tafenoquine to Prevent Relapse of *Plasmodium vivax* Malaria (DETECTIVE, 2019): https://www.nejm.org/doi/full/10.1056/NEJMoa1710775
3. Tafenoquine versus Primaquine to Prevent Relapse of *Plasmodium vivax* Malaria (GATHER, 2019): https://www.nejm.org/doi/full/10.1056/nejmoa1802537
4. Neurological and psychiatric safety of tafenoquine in *Plasmodium vivax* relapse prevention: a review (2020): https://malariajournal.biomedcentral.com/articles/10.1186/s12936-020-03184-x
5. Tafenoquine: a toxicity overview (2020): https://www.tandfonline.com/doi/full/10.1080/14740338.2021.1859476
6. 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 (2021): https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(21)00328-X/fulltext
7. Drug-induced corneal deposits: an up-to-date review (2022): https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8961126/
8. Tafenoquine co-administered with dihydroartemisinin–piperaquine for the radical cure of *Plasmodium vivax* malaria (INSPECTOR): a randomised, placebo-controlled, efficacy and safety study (2023): https://www.vivaxmalaria.org/resources/tafenoquine-co-administered-with-dihydroartemisinin%E2%80%93piperaquine-for-the-radical-cure-of
9. Operational feasibility of Plasmodium vivax radical cure with tafenoquine or primaquine following point-of-care, quantitative glucose-6-phosphate dehydrogenase testing in the Brazilian Amazon: a real-life retrospective analysis (2024): https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(23)00542-9/fulltext
10. Operational effectiveness of tafenoquine and primaquine for the prevention of Plasmodium vivax recurrence in Brazil: a retrospective observational study (2024): https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(24)00074-4/fulltext

Primaquine

1. Haemolysis in G6PD Heterozygous Females Treated with Primaquine for *Plasmodium vivax* Malaria: A Nested Cohort in a Trial of Radical Curative Regimens (2017): https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002224
2. Primaquine alternative dosing schedules for preventing malaria relapse in people with *Plasmodium vivax* (2020): https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012656.pub3/full

3. Primaquine dose and the risk of haemolysis in patients with uncomplicated *Plasmodium vivax* malaria: a systematic review and individual patient data meta-analysis (2023): https://www.sciencedirect.com/science/article/pii/S1473099923004310?via%3Dihub
4. Effect of primaquine dose on the risk of recurrence in patients with uncomplicated *Plasmodium vivax*: a systematic review and individual patient data meta-analysis (2023): https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(23)00430-9/fulltext

Annex 3: STANDARD G6PD point-of-care quantitative test by SD Biosensor

INTERPRETATION OF TEST RESULT

Male		Female	
G6PD Deficient*	≤ 4.0 U/g Hb	G6PD Deficient*	≤ 4.0 U/g Hb
G6PD Normal	≥ 4.1 U/g Hb	G6PD Intermediate**	4.1-6.0 U/g Hb
		G6PD Normal	≥ 6.1 U/g Hb

*Deficient was determined during clinical evaluation as approximately 30% of the adjusted male median of specimens tested.
**Intermediate was determined during clinical evaluation as females with activity greater than 30% and less than or equal to 70% of the adjusted male median.

[1] World Health Organization (WHO). *WHO World malaria report.* Geneva: WHO; 2023. https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2023.
[2] World Health Organization (WHO). *WHO guidelines for malaria*. Geneva: WHO; 2023. https://app.magicapp.org/#/guideline/LwRMXj/section/jlyQVL.
[3] US FDA approves Krintafel (tafenoquine) for the radical cure of P. vivax malaria. London, Philadelphia, and Geneva: Medicines for Malaria Venture and, GSK;. US FDA approves Krintafel (tafenoquine) for the radical cure of P. vivax malaria. July 20, 2018. https://www.mmv.org/sites/default/files/uploads/docs/press_releases/US_FDA_approves_Krintafel.pdf.
[4] Medicines for Malaria Venture. Single-dose Kozenis (tafenoquine) approved for children with Plasmodium vivax malaria by Australian Therapeutic Goods Administration. Geneva: Medicines for Malaria Venture; March 22, 2022. https://www.mmv.org/newsroom/news-resources-search/single-dose-kozenis-tafenoquine-approved-children-plasmodium-vivax#:~:text=Medicines%20for%20Malaria%20Venture%20(MMV,vivax)%20malaria.
[5] Partnership for Vivax Elimination (PAVE). *Plasmodium vivax tool brief: Point-of-care G6PD diagnostics.* Geneva and Seattle: PATH and MMV; 2022. https://www.vivaxmalaria.org/resources/plasmodium-vivax-tool-brief-point-of-care-g6pd-diagnostics.
[6] Chu CS, White NJ. Management of relapsing *Plasmodium vivax* malaria. *Expert Review of Anti-Infective Therapy*. 2016;14(10):885-900. https://doi.org/10.1080/14787210.2016.1220304.
[7] White, N.J. Determinants of relapse periodicity in *Plasmodium vivax* malaria. *Malaria Journal.* 2011;10-297. https://doi.org/10.1186/1475-2875-10-297.
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[9] The Global Fund to Fight AIDS, Tuberculosis and Malaria. *List Of Malaria Pharmaceutical Products classified according to the Global Fund Quality Assurance Policy.* Geneva: Global Fund; 2023. https://www.theglobalfund.org/media/11151/psm_productsmalaria_list_en.pdf
[10] Commons RJ, Rajasekhar M, Edler P, et al. Effect of primaquine dose on the risk of recurrence in patients with uncomplicated *Plasmodium vivax*: a systematic review and individual patient data meta-analysis. *The Lancet Infectious Diseases.* 2023;S1473-3099(23)00430-9. https://doi.org/10.1016/S1473-3099(23)00430-9.

[11] Rajasekhar M, Simpson JA, Ley B, et al. Primaquine dose and the risk of haemolysis in patients with uncomplicated *Plasmodium vivax* malaria: a systematic review and individual patient data meta-analysis. *The Lancet Infectious Diseases.* 2023;S1473-3099(23)00431-0. https://doi.org/10.1016/S1473-3099(23)00431-0.
[12] Sutanto I, Soebandrio A, Ekawati LL, et al. Tafenoquine co-administered with dihydroartemisinin-piperaquine for the radical cure of *Plasmodium vivax* malaria (INSPECTOR): a randomised, placebo-controlled, efficacy and safety study. *The Lancet Infect Diseases.* 2023;23(10):1153-1163. doi: 10.1016/S1473-3099(23)00213-X.
[13] Vélez ID, Hien TT, Green JA, 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. *The Lancet Child & Adolescent Health*. 2022 Feb;6(2):86-95. doi: 10.1016/S2352-4642(21)00328-X.
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