Theoretical Framework and Background

Overview of vivax malaria

Plasmodium vivax (P. vivax) accounts for approximately 4.5 million cases of malaria worldwide and predominates in areas where control programs for this infection have been intensified and the prevalence of the disease is low (1,2). In the Americas, *P. vivax* is the strain responsible for 78.6% of malaria cases (2)

P. vivax has biological characteristics that hinder its elimination. One of the most important is the ability to develop a hepatic stage, the hypnozoite, which remains latent in the liver and reactivates after several weeks or months following treatment for a malaria episode. This phenomenon leads to a type of infection recurrence called relapse, characterized by the reappearance of parasitemia, usually accompanied by clinical manifestations (1,4). Relapses occur with gametocytes, which contribute to maintaining the transmission of this species to the vector and subsequently to other susceptible hosts (1). Furthermore, hypnozoites are undetectable by diagnostic methods, and evidence in many endemic regions suggests that they are not always eliminated with antimalarial treatment. This complicates the design of strategies to prevent relapses (5).

Treatment of *P. vivax* Infection

For *P. vivax* infection, a combined treatment of two antimalarials is used: the first one to eliminate the blood forms, and the second one against the hepatic forms. Chloroquine (a 4-aminoquinoline) is the most widely used drug as a blood schizonticide, which shows an adequate therapeutic response in many regions. In places with reported therapeutic failure, artemisinin-based combination therapies are used (4,6,7). To prevent relapses, primaquine, an 8-aminoquinoline, is used. This drug not only has activity against the gametocytes of various *Plasmodium* species that infect humans, but also against the hypnozoites. The effective therapeutic action of primaquine leads to radical cure, meaning it will prevent the occurrence of relapses. However, it has the disadvantage of being contraindicated in pregnant women, lactating mothers, children under 6 months, and individuals with glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency; in the latter case, due to the risk of severe hemolysis (8,9).

The evaluation of the therapeutic response to primaquine is complex because studies usually have to be carried out in areas with malaria transmission, where accurate discrimination between a relapse and a reinfection is not possible (10,11). Therefore, the therapeutic efficacy of primaquine is assessed based on recurrences (which includes both relapses and reinfections) (11,12). In this regard, the standard regimen of primaquine (0.25 mg/kg/day for 14 days, equivalent to a total dose of 3.5 mg/kg) has shown poor efficacy in preventing recurrences within 6 months, with recurrence incidence rates close to 30% when the treatment is administered under supervision (11,12). In the scenario of unsupervised treatment, this recurrence rate within 6 months is close to 50% (13). Therapeutic

alternatives to prevent *P. vivax* malaria recurrences are limited. They include administering a higher dose of primaquine under complete supervision (14 days or 7 days, but this last dosing scheme has not yet been approved by the WHO) or using tafenoquine, another 8-aminoquinoline recently approved in some countries (12,14) which is better than unsupervised treatment with primaquine.

Tafenoquine offers the advantage of being administered in a single dose, which promises good adherence (14). However, its use has been approved only in individuals over 16 years old. It maintains the same contraindications as primaquine, and its effect has only been evaluated in patients without G6PD deficiency (15). A high dose of primaquine (>3.5 mg/kg) also poses even a higher risk to the population with this deficiency. Therefore, having a properly tolerated and effective treatment for the radical cure of *P. vivax* requires screening for G6PD deficiency and a treatment algorithm based on the deficiency status (8,16). The WHO, in its malaria treatment guidelines, recommends conducting tests to detect G6PD deficiency before administering primaquine treatment for the radical cure of *P. vivax* (17); however, each country has autonomy in adopting this directive. In most countries, the standard regimen of primaquine (3.5 mg/kg over 7 or 14 days) is currently used without prior G6PD deficiency screening (2). Recent studies have shown there is a risk of haemolysis even for the dose of 3.5 mg/kg (18, 19); therefore, therefore, ideally all the patients before receiving an 8-aminoquinoline should be tested for G6PD whatever is the dose of primaquine used. When the G6PD test is available, the recommendation is to treat patients with enzymatic activity deficiency with a regimen of 0.75 mg/kg of primaquine weekly for 8 weeks (20).

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

G6PD deficiency is an X-chromosome-linked genetic disorder. More than ~~180~~ 230 genetic variants associated with G6PD deficiency have been reported, most of which have asymptomatic phenotypes (21). Different studies have identified mutations associated with varying levels of enzymatic activity. It has been established that African allelic variants, referred to as variant A, are the most common worldwide and in the Americas. Variant A, in turn, has a subclassification as A+, which can be associated with either normal or very mild deficient activity, while variant A– has abnormal enzymatic activity ranging from 8 to 20%. The Mediterranean variant is considered more severe, with <5% of normal activity (22).

It is estimated that over 400 million people worldwide have some degree of G6PD deficiency, with the distribution of this condition being highly variable, depending on the region and ethnic group. The highest prevalence rates of the enzyme deficiency condition have been reported globally in African countries (20%), the Mediterranean (4 - 30%), and Southeast Asia (10 - 20%) (23). Furthermore, it has been observed that in malaria-endemic regions, the allelic frequency of the gene determining G6PD deficiency is present in about 8% of the population (approximately 220 million men and 133 million women) (23).

Because G6PD deficiency is caused by an alteration on the “X” sex chromosome, men can have two genotypes: either hemizygous normal or hemizygous deficient, while women may be homozygous normal, homozygous deficient, or heterozygous, and may or may not be deficient due to the phenomenon of lyonization (inactivation of one X chromosome) (24). These five genotypes in both men and women may lead to three phenotypes (17) (Figure 1):

1) Normal G6PD Activity: Men and women with enzymatic activity in red blood cells >80%.
2) Deficient G6PDH Activity: Hemizygous men for a deficient allele, who have enzymatic activity in red blood cells <10% of normal. Women with enzymatic activity in red blood cells <30% of normal. These women can be homozygous for the deficient allele, biallelic or heterozygous for a deficient allele with predominance of red blood cells with G6PD deficiency.
3) Intermediate G6PD Activity: Only heterozygous women with one deficient allele and one normal allele. They have enzymatic activity between 30% and 80% of normal.

Figure 1. Graphical representation of genotypes and phenotypes for glucose-6-phosphate dehydrogenase deficiency.

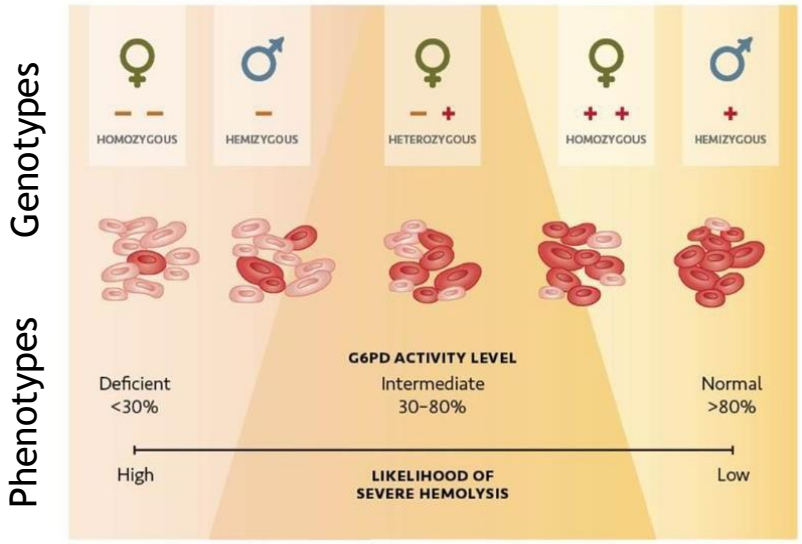

Image taken from: Domingo G y cols (22).

Diagnosis of Glucose-6-Phosphate Dehydrogenase Deficiency

For the diagnosis of G6PD deficiency, various qualitative and quantitative methods are available, some of which can be applied at the point of care (17). Qualitative tests are used as screening and are the most commonly used, an example of these is the fluorescent spot test. This test measures the presence of the NADPH cofactor through a chemical reaction and fluorescence. This method allows the classification of blood samples from men and women as either normal or deficient, and provides visual qualitative results within minutes. However, as it requires trained personnel and equipment such as a long-wave ultraviolet light lamp, a water bath or heat block, a darkroom, reagents, and controls, it is not suitable for field use (17). Another important disadvantage of qualitative tests is that they provide a discriminatory threshold of enzymatic activity in percentages between 30-40% of normal G6PD activity. However, the sensitivity of the test varies according to enzymatic activity, meaning the test can accurately identify a hemizygous man for the gene with activity <30% as deficient, while a heterozygous woman with enzymatic activity of 50% could be classified as normal, which could lead to a pro-hemolytic event with the administration of any 8-aminoquinoline.

Quantitative methods like spectrophotometry are considered the reference methods for detecting G6PD deficiency (26). These methods indirectly measure the formation of NADPH as a result of G6PD enzymatic activity. These tests normalize enzyme activity results with the concentration of hemoglobin in the analyzed red blood cells. As disadvantages of these methods, it can be mentioned that they require controlled temperature, specialized equipment, highly trained personnel, and quality controls to validate the results. With these tests, a specific value of enzyme activity is obtained, which can be interpreted within a range as normal, intermediate, or deficient (26,27).

Recently, colorimetric enzyme assays have been developed for the semi-quantitative measurement of G6PD activity, such as the STANDARD™ G6PD test (SDBiosensor, Republic of Korea), which may or may not normalize the enzyme activity result, according to the total hemoglobin concentration in capillary total blood (finger prick) or anticoagulated venous whole blood. These methods analyze the sample by illuminating it with LED light, determining the average light concentration, which is reflected in the sample application area. These are methods that can be performed in the field and are of low complexity. These tests can detect patients with intermediate G6PD activity between 30% and 70%, the thresholds required to identify heterozygous women (27).

The STANDARD™ G6PD is a field-applicable test that, compared to other tests, offers the possibility of knowing the degree of deficiency of this enzyme based on a semi-quantitative determination of enzymatic activity, using a venous or capillary sample (28). Compared to the gold standard (spectrophotometry), this test performs well, with sensitivity and specificity values of 100% (92.3–100.0) and 97% (95.2–98.2) respectively when using a capillary sample (28).

Implementation of the STANDARD™ G6PD Test in the Context of *P. vivax* Malaria Treatment

While the STANDARD™ G6PD test performs well, it has not yet been globally implemented in the patient care process for *P. vivax* malaria cases that will receive drugs that may cause hemolysis, such as primaquine or tafenoquine. The science of implementation defines four major phases for implementing an evidence-based intervention: exploration, preparation, implementation, and sustainment of the intervention (29,30). In this case, the STANDARD™ G6PD test is considered a crucial component of the new treatment regimen for *P. vivax* malaria (evidence-based intervention).

Each of the implementation phases requires the evaluation of implementation outcomes (31) and the assessment of barriers and facilitators that influence the occurrence of these outcomes. These include the intervention's characteristics, the external environment, the internal environment, individual characteristics, and the implementation process (30). For an evidence-based intervention in the exploration stage, it is recommended to assess feasibility, acceptability, and suitability for future adoption of the intervention; in the preparation phase, adoption and cost; in the implementation phase, fidelity and penetration: and in the sustainability phase, sustainability should be considered (31,33).

Another crucial aspect in the context of implementing an intervention or program is the delivery strategy to potential implementers and end users. Identifying contextual determinants (barriers and facilitators) enables the design of pertinent strategies (34). In the context of implementing the STANDARD™ G6PD test as part of a program for managing *P. vivax* malaria, the training program for

community leaders and healthcare workers in using the test is critical to ensure its acceptability and correct use (35).

The PAVE consortium aims to increase access to radical cure for *P. vivax* malaria through coordinated efforts with governments of endemic countries for this disease. PAVE intends to expand access to both new and existing radical cure antimalarials and related diagnostic tests in *P. vivax* endemic countries, such as Colombia. This way, PAVE hopes to accelerate the introduction and expansion of access to well tolerated treatments for the radical cure of *P. vivax* malaria. This includes drugs for both blood stages (like Chloroquine) and liver stages, like tafenoquine (TQ), as well as malaria and G6PD diagnostic tests, such as the rapid STANDARD™ G6PD test (36).

Feasibility, acceptability, and cost studies for the STANDARD™ G6PD test are being conducted in countries including Brazil, Peru, Ethiopia, India, Afghanistan, Indonesia, Vietnam, Thailand, Myanmar, Laos, and Bangladesh (35,37–43). For Latin America, Brazil has just completed a study evaluating adherence to the new diagnostic and treatment flowchart with G6PD and tafenoquine testing in two municipalities. In Peru, a similar study has started in August 2023.

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