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Chloroquine Therapy and *G6PD* Genotype

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Introduction

Chloroquine is used for the treatment of uncomplicated malaria and extra-intestinal amebiasis. Malaria is caused by infection of *Plasmodium* parasites. Chloroquine is active against the erythrocytic forms of susceptible strains of *Plasmodium falciparum (P. falciparum)*, *Plasmodium malariae (P. malariae)*, *Plasmodium ovale (P. ovale)*, and *Plasmodium Vivax (P. vivax)*. Chloroquine is not active against the gametocytes and the exoerythrocytic forms including the hypnozoite stage (*P. vivax* and *P. ovale*) of the *Plasmodium* parasites. Additionally, resistance to chloroquine and hydroxychloroquine has been reported in *Plasmodium* species, thus chloroquine therapy is not indicated if the infection arose in a region with known resistance. Chloroquine is used in first-line treatment of *P. vivax* malaria with primaquine. Studies have indicated chloroquine is effective against the trophozoites of *Entamoeba histolytica (E. histolytica)*, which causes amebic dysentery, or amebiasis. (1) Chloroquine also has off-label uses for treatment of rheumatic diseases and has been investigated as a potential antiviral therapy as well as an adjuvant chemotherapy for several types of cancer. (2, 3, 4, 5)

Chloroquine accumulates in cellular acidic compartments such as the parasitic food vacuole and mammalian lysosomes, leading to alkalinization of these structures. This change in pH can impair the action of enzymes responsible for the formation of hemozoin by the parasite from ingestion of the host's hemoglobin; this reaction occurs in the parasitic vacuole (6). Thus, chloroquine targets the blood-stage of the malaria parasites but cannot eliminate dormant hypnozoites and must be administered with a drug that targets the dormant parasitic form (1). Chloroquine, developed in the 1940s, has been superseded as the first-line recommended antimalarial therapy by both the US Centers for Disease Control (CDC) and World Health Organization (WHO), with the exceptions of during the first trimester of pregnancy or for malarial prophylaxis of a pregnant individual who is also deficient for glucose-6-phosphate dehydrogenase (G6PD) (7, 8). Among antimalarial medications, chloroquine is less likely than other medicines to cause hemolysis in G6PD-deficient individuals; however, the FDA-approved drug label states there is still a risk of hemolysis (Table 1) (1). In contrast, the Clinical Pharmacogenetics Implementation Consortium (CPIC) performed a systematic review of the available clinical literature and found low-to-no risk of acute hemolytic anemia for individuals with G6PD deficiency who take hydroxychloroquine or chloroquine (9) (Table 2). It should be noted that G6PD deficiency has a range of severity; CPIC advises caution for all medications when used by an individual with a severe G6PD deficiency with chronic non-spherocytic hemolytic anemia (CNSHA).

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Table 1: The FDA Drug Label for Chloroquine Phosphate (2020)

Phenotype	Precautions
G6PD deficiency	Chloroquine may cause hemolysis in G6PD deficiency. Blood monitoring may be needed as hemolytic anemia may occur in association with other drugs that cause hemolysis.

G6PD - Glucose-6-phosphate dehydrogenase. This FDA table is adapted from (1).

Table 2: The CPIC Guidelines for Chloroquine based on G6PD Phenotype

Predicted G6PD phenotype based on genotype	Implication for phenotypic measures	Therapeutic recommendation	Classification of recommendation[a]	Evidence level[a]
Normal	Low-to-no risk of acute hemolytic anemia	No reason to avoid low-to-no risk drugs based on G6PD status	Strong	Weak
Deficient	Low-to-no risk of acute hemolytic anemia	No reason to avoid low-to-no risk drugs based on G6PD status at standard doses	Moderate	Weak (High)[b]
Deficient with CNSHA	High-risk of acute exacerbation of chronic hemolysis	Use all drugs cautiously in this group; if a drug is used, close monitoring for acute exacerbation of chronic hemolysis is recommended	Optional	Weak
Variable	Low-to-no risk of acute hemolytic anemia	No reason to avoid low-to-no risk drugs based on G6PD status at standard doses	Moderate	Weak
Indeterminate	Unknown risk of acute hemolytic anemia	To ascertain G6PD status, enzyme activity must be measured. Drug use should be guided per the recommendations based on the activity-based phenotype	Moderate	Weak

CNSHA - Chronic non-spherocytic hemolytic anemia; G6PD - glucose-6-phoshate dehydrogenase
[a] Rating scheme and evidence level based on clinical data from (9) Supplement.
[b] One preclinical study found no evidence of hemolysis in a humanized mouse model of G6PD deficiency.
This table is adapted from (9).

Drug: Chloroquine

Chloroquine is a 4-aminoquinoline used for the treatment of susceptible strains of malaria and extra-intestinal amebiasis caused by trophozoites of *E. histolytica* (1). It has off-label uses in rheumatic diseases, the treatment and prophylaxis of Zika virus, and it has been investigated for treatment of human immunodeficiency virus (HIV) (10, 11, 12, 13). However, in many cases hydroxychloroquine, a chloroquine derivative, is used more often for rheumatic conditions. Chloroquine has also been investigated as an adjuvant anticancer therapy (14, 15, 16). Because of its widespread use to treat and prevent malaria between the 1940s and 1980s, resistance to chloroquine has arisen in many strains of the malaria-causing parasite in several endemic areas (17). Additional antimalarial medications have since been developed and can be used to treat those resistant strains. Following recommendations by the WHO, chloroquine is no longer the first line therapy, having been replaced by artemisinin-based combination therapies (8).

Chloroquine inhibits the heme polymerase enzyme in the malarial parasite due to neutralizing the pH of the vacuole, resulting in a fatal accumulating of toxic heme within the parasite (10). Within human cells, chloroquine passively diffuses into subcellular structures important for protein synthesis and cellular waste removal: Golgi vesicles, endosomes, and lysosomes. The lysosome is the site of cellular autophagy, the mechanism whereby cells clear damaged organelles and protein masses as well as degrade foreign material. The

lysosome is an acidic compartment and once inside, chloroquine becomes protonated and trapped, causing the pH of the lysosome to rise. This inhibits autophagy and is the mechanistic basis for its use as an adjuvant anticancer therapy with standard chemical and radiation oncology treatments. (14, 15, 18, 19) Chloroquine also affects innate and adaptive immunity, acting at several key points of immune regulation. Chloroquine and hydroxychloroquine both inhibit recognition of nucleic acids by the toll-like receptors, the major histocompatibility complex class II-mediated antigen presentation, inflammation induced cell proliferation and antiphospholipid antibody activity, making them useful for the treatment of autoimmune disorders such as systemic lupus erythematous (20).

Chloroquine phosphate is not indicated for use in the treatment of complicated malaria, nor should it be used in individuals with known hypersensitivity to 4-aminoquinoline compounds. Concomitant medication with an 8-aminoquinoline is necessary to treat the hypnozoite stage of certain *Plasmodium* parasites' life cycle (see below for more details). Per the FDA-approved label, use of chloroquine phosphate for any condition other than acute malaria is contraindicated in the presence of retinal or visual changes of any etiology (1). Acute malaria therapy with chloroquine requires only 3 days to complete the full course of medication (1).

In March of 2020, hydroxychloroquine and chloroquine were granted emergency use authorization by the U.S. Food and Drug Administration for the treatment of coronavirus disease 2019 (COVID-19) caused by infection with the severe acute respiratory syndrome coronavirus 2 virus (21). This authorization was revoked on 15 June 2020 due to the risk of cardiac adverse events and other potential adverse reactions, which were determined to outweigh the potential benefit of these medications in treating COVID-19 (22).

Chronic chloroquine use may cause irreversible retinal damage. If chloroquine is to be prescribed for an extended period, the FDA-approved drug label states that a baseline visual exam must be taken within the first year of therapy to monitor for any changes in vision. The baseline exam should include "best corrected distance visual acuity, an automated threshold visual field (VF) of the central 10 degrees (with retesting if an abnormality is noted), and spectral domain optical coherence tomography (SD-OCT)." These exams should be performed annually for individuals when daily doses of chloroquine phosphate are greater than 2.3 mg/kg of actual body weight (bw), durations of use greater than 5 years, subnormal glomerular filtration, or use of some concomitant drug products such as tamoxifen citrate. Individuals without these risk factors should have their vision assessed once every 5 years. (1)

The American Academy of Ophthalmology (AAO) similarly advises that in addition to the automatic visual field exams, SD-OCT should also be performed (23) and recently updated their recommended dosage to no more than 2.3 mg/kg per day for rheumatoid condition therapy (24). The Royal College of Ophthalmologists in the United Kingdom has also published recommendations for visual screening with regular monitoring for individuals on prolonged chloroquine and hydroxychloroquine therapy (25). If ocular toxicity is suspected, discontinue use immediately, though visual changes may continue to progress after withdrawal due to the prolonged systemic half-life of chloroquine. (16)

It should be noted that in individuals of Asian descent, retinal toxicity may present first outside of the macula, thus the FDA recommends the VF screening be performed in the central 24 degrees (rather than 10) in this population. (1) The AAO also recommends SD-OCT testing should look beyond the central macula in Asian individuals (23). The specific mechanism underlying this difference in disease presentation is unknown, though genetics are suspected to play a role (23). It is hypothesized that the mechanism of retinal damage due to prolonged chloroquine therapy is due to its ability to bind to the melanin pigment in the iris, ciliary body, and retinal pigment epithelium (16, 26, 27).

Chloroquine may result in additional adverse effects on cardiac, neurological, and muscle tissues (20). Cardiac tissue toxicity can result in cardiomyopathy with conduction defects including prolonged QT interval, Torsades de pointes, and ventricular arrhythmias. Some studies have indicated that QT prolongation can present within 3

to 5 days of treatment with chloroquine or hydroxychloroquine, though arrythmias and conduction disorders are more common with chloroquine versus hydroxychloroquine (20, 28). The arrythmia risk is dose dependent and increased by co-medication with other arrhythmogenic drugs such as amiodarone or moxifloxacin. Neuromuscular toxicity is rare, but there have been reports of proximal symmetric muscle deficits and polyneuropathies (20). Chloroquine can also cause severe hypoglycemia, both with and without concomitant antidiabetic medication. Hypoglycemia is an intrinsic reaction to the drug but can also be triggered by the nutritional status of the individual with malaria. Auditory effects have also been reported, as such the FDA advises that chloroquine should be administered with caution in individuals with pre-existing auditory damage and to immediately discontinue the medication in the event of any defects in hearing. Additional side effects or risks include acute extrapyramidal disorders, muscle weakness, increased risk of psoriatic attack or worsening of porphyria, and a potential elevated risk of convulsions in individuals with a history of epilepsy. (1) Cutaneous toxicity has also been reported; pruritus has been reported in up to half of treated individuals from several studies (29) and pigmentation changes have also been reported (20). Much of these off-target tissue toxicities are predicted to result from the alkalinization of lysosomes, modulation of immune reactions and, in some cases, off-target activation of cellular receptors (20).

There have also been reports of adverse psychiatric side effects of chloroquine use. These symptoms include insomnia, mania, paranoia and persecutory delusions and auditory and visual hallucinations (30). The incidence of these psychoses are rare, occurring once per hundreds to thousands of individuals prescribed chloroquine and mefloquine—another antimalarial medication, and is not common in the treatment of uncomplicated malaria (31). Of note, there seems to be no correlation between chloroquine-induced psychiatric symptoms and pre-existing familial or personal predisposition to mental disorders (32).

The FDA-approved label states that individuals with G6PD enzyme deficiency may be predisposed to hemolysis during chloroquine therapy (1). Therapy includes treatment for active, uncomplicated malaria that requires administration of 1.5 g base over 3 days in adults and 25 mg base/kg bw in infants and children. Prophylaxis therapy consists of a weekly dose of 300 mg base for adults or a weekly dose of 5 mg base per kg bw in children (1). The CDC advises that individuals with G6PD deficiency who may not tolerate other antimalarial medications may be prescribed a prophylactic dose of chloroquine for one year following acute malarial infection with *Plasmodium* species with hypnozoites, as most relapses from reactivation occur within this timeframe (33). As of 2023, chloroquine is not available in the Canadian market, however the last active label from Health Canada advised caution when using chloroquine in individuals with G6PD deficiency (34). In contrast, the drug regulatory agency of Switzerland (Swissmedic) states that G6PD deficiency is a contraindication for chloroquine therapy due to symptoms of hemolytic anemia and favism (35).

Chloroquine is metabolized by the cytochrome P450 family of enzymes. First, chloroquine is N-dealkylated to N-desethylchloroquine, which is an active metabolite (36). This is achieved primarily through CYP2C8 and CYP3A4 mediated metabolism, with a lesser contribution from the enzymes CYP3A5, CYP2D6, and even less by CYP1A1 (10, 36). Chloroquine and desethylchloroquine have elimination half-lives of 20–60 days, primarily via renal excretion. Much of the absorbed chloroquine is bound by albumin and P-glycoprotein and a considerable amount of chloroquine is stored in tissues, resulting in a large volume of distribution (1, 36). Multiple intrinsic factors can impact the pharmacokinetic parameters of chloroquine including age, pregnancy status, body weight, as well as *CYP* genetic variation (36, 37, 38). Although chloroquine can freely diffuse into cells, it is also a substrate of several transporter proteins. Chloroquine is a substrate, inhibitor, and inducer of the multidrug resistance-associated protein 1 (MRP1) and a substrate of organic anion transporting proteins (OATPs) (36). Various drug interactions have been documented with chloroquine, either based on absorption or metabolism. Ampicillin, cyclosporine, praziquantel, and cimetidine may all interact with chloroquine and these drugs may have altered metabolism and plasma concentrations when taken concurrently with chloroquine (1).

Chloroquine overdose is a serious risk, particularly for children with accidental ingestion, as chloroquine is rapidly absorbed. The FDA label states that even one gram of chloroquine may be fatal in children (3 years of age) (1). Toxicity symptoms include nausea, vomiting, headache, drowsiness, visual disturbances, cardiovascular collapse, convulsions, hypokalemia, cardiac arrythmia and conduction defects, and sudden, potentially fatal respiratory and cardiac arrest; these symptoms may present within minutes of overdose. Immediate medical attention is required. Thus, it is strongly advised by the FDA-approved label to keep chloroquine phosphate out of reach of children, as these individuals are particularly sensitive to 4-aminoquinoline compounds (1).

Human studies have not shown an increase in the rate of birth defects or spontaneous abortions associated with chloroquine use by pregnant mothers, nor evidence of fetal ocular toxicity. (1, 39) The CDC states that for pregnant women with uncomplicated malaria caused by *P. malariae, P. ovale*, or chloroquine-sensitive *P. vivax* or *P. falciparum*, treatment with hydroxychloroquine or chloroquine is recommended (33). Chloroquine is also the recommended alternative therapy during pregnancy by the WHO for infection with sensitive *Plasmodium* strains (8). Furthermore, the CDC recommends continued chloroquine prophylaxis for individuals with *P. vivax* or *P. ovale* infection for the duration of pregnancy. If, upon delivery, the mother intends to breastfeed, the infant should be tested for G6PD deficiency. If neither the infant nor mother are G6PD deficient, primaquine phosphate is the recommended therapy for the mother (tafenoquine is not recommended during breastfeeding). Otherwise, women who cannot take tafenoquine or primaquine due to G6PD deficiency should continue weekly chloroquine prophylaxis for one year following acute malarial infection (33). Small amounts of chloroquine are excreted in breast milk. A once per week dosage is not sufficient to cause harm to a nursing infant, nor is it sufficient to provide protection from malaria (40). Thus, infants at risk of malaria exposure who are breastfed still require prophylaxis. One study reported a decrease in viral HIV loads in breast milk of HIV-infected women who were treated with chloroquine as compared with women who were treated with a combination of sulfadoxine and pyrimethamine (41).

Disease: Malaria

Malaria is a serious tropical disease caused by a parasite (*Plasmodium*) that spreads to humans by infected mosquitos. The only available vaccine is moderately effective and acts only against *the P. falciparum* species (42). Widely recommended antimalarial drugs such as mefloquine can be used for prevention, which is known as chemoprophylaxis. The type of chemoprophylaxis recommended depends upon the individual taking the prophylaxis (namely: age, pregnancy status, concurrent medication use, and medical comorbidities) and the nature of travel –– specifically, the countries traveled to, the length of stay, the species of *Plasmodium* that are most prevalent, and the level of drug resistance.

Despite chemoprophylaxis, travel to malaria-endemic areas is not without risk. Individuals at elevated risk for malaria complications include pregnant women (33) and adults who have had their spleen removed (43). If travel cannot be avoided, chemoprophylaxis should be combined with additional precautions to avoid mosquito bites, such as bed nets and repellents. In 2021, the WHO estimated 247 million cases of malaria occurred worldwide, and malaria was responsible for at least 619,000 deaths. (44)

Malaria is found in over 100 countries and occurs throughout most tropical regions in the world. These regions include large parts of Africa, Asia, Central and South America, and parts of the Middle East and Pacific islands (45, 46). Individuals who are heterozygous carriers for sickle cell disease or G6PD deficiency have a protective advantage against malaria, and as a result, the frequency of such genetic conditions is higher in countries where malaria is endemic (47).

Malaria is transmitted to humans by the bite of an infected *Anopheles* mosquito. Only female mosquitos spread the infection (females feed on human blood, males feed on nectar). Although malaria can also be spread by sharing contaminated needles or via a contaminated blood transfusion, these are rare means of transmission. (48)

There are several different *Plasmodium* species, but only a few species cause the most malaria cases:

- *P. falciparum*
  - The most common cause of malaria, and death from malaria
  - Predominates in sub-Saharan Africa
  - Also found in regions of Australasia (Papua New Guinea, Southeast Asia), and the Caribbean (Haiti and the Dominican Republic)
- *P. vivax*
  - A common cause of malaria outside of Africa
  - Most frequent species found in Central and South America
  - Parasite has a dormant, hypnozoite stage
  - Early gametocytes that infect mosquitos
- *P. malariae*
  - Less common
  - Found in most areas where malaria is endemic
- *P. ovale*
  - Less common
  - Parasite has a dormant, hypnozoite stage
- *P. knowlesi*
  - Less common
  - Found in some areas of Southeast Asia

The first stage of malaria infection begins when an infected mosquito bites the human host. Typically, mosquitos bite at dusk, or during the night. As the mosquito feeds, infective parasite sporozoites (the motile spore-like stage in the life cycle of this parasitic sporozoan, which is the infective agent) are inoculated into humans. The sporozoites travel to the liver, where they invade liver cells and asexually reproduce to form schizonts. The liver schizonts contain daughter merozoites. This process is asymptomatic, and because it occurs outside of the red blood cell (erythrocyte), it is known as the exoerythrocytic stage. (49)

Some species of the parasite (*P. vivax* and *P. ovale*) have an additional dormant stage in the liver. The parasite exists as hypnozoites, which can stay in the liver for weeks or months without causing any clinical symptoms.

The second stage of malaria infection is the erythrocytic stage. It begins when the liver schizonts rupture and release the daughter merozoites into the bloodstream. The merozoites invade red blood cells, digest hemoglobin, produce a toxic metabolite (hemozoin), and damage red blood cell membranes. Infected, brittle red blood cells are rapidly broken down (hemolysis) and if too many damaged red blood cells get trapped in the spleen, the spleen can rapidly enlarge (splenic sequestration). Notably, *P. vivax* preferentially infects the immature reticulocytes rather than mature erythrocytes due to expression of reticulocyte-specific receptors; G6PD levels are higher in reticulocytes than erythrocytes, which may provide more protection against oxidative stress for the *P. vivax* parasite (50, 51).

Some of the daughter merozoites differentiate into male or female gametocytes (sexual forms). When they are ingested by a mosquito, they mature, fertilize, reproduce, and develop into sporozoites. When the mosquito feeds again, the sporozoites are inoculated into another human host and the cycle of malaria transmission is complete.

The erythrocytic stage of malaria is usually associated with fever, and malaria should always be suspected in anyone with a fever who has recently returned from a malaria-endemic region, even if antimalarial chemoprophylaxis was correctly followed. Other symptoms and signs include nausea, vomiting, abdominal pain, tachycardia (fast heart rate), diaphoresis (sweating), chills, and myalgia (muscle pain). The complications of

malaria infection include severe anemia, cerebral malaria, and multi-organ failure. Without correct diagnosis and prompt treatment, malaria can be fatal.

Gene: *G6PD*

The G6PD enzyme is encoded by the *G6PD* gene, which is located on chromosome Xq28. As such, males are hemizygous for one *G6PD* allele, making them more susceptible to this X-linked disorder. Females randomly inactivate one X chromosome during development, resulting in a mosaic expression of either one X chromosome or the other in their somatic cells. This mosaicism can occur in the hematopoietic progenitor cells that give rise to red blood cells, resulting in mixed expression of *G6PD* alleles. Females with Turner syndrome (45, X) have only one X chromosome and thus are also hemizygous for the *G6PD* gene. Males with Klinefelter syndrome have an additional X chromosome (47, XXY) and therefore 2 *G6PD* alleles. Thus, it is important to consider the number of X chromosomes for an individual when determining *G6PD* genotype or phenotype.

Glucose-6-phosphate dehydrogenase deficiency affects 400 million people worldwide, with a worldwide prevalence of approximately 5% (52). Glucose-6-phosphate dehydrogenase deficiency appears to be protective against malaria infection leading to a higher prevalence (more than 25%) in countries where malaria is or once was endemic (for example, tropical Africa, tropical and subtropical Asia, the Middle East, and some parts of the Mediterranean) (53, 54, 55). In the US, G6PD deficiency is more common among African Americans, affecting approximately 12% (56).

The G6PD enzyme catalyzes the first step in the hexose monophosphate shunt (HMP) pathway, which converts glucose to pentose sugars for nucleic acid synthesis. In this step nicotinamide adenine dinucleotide phosphate (NADP+) is reduced to NADPH, which protects cells from oxidative stress. In mature red blood cells, the HMP pathway is the only source of NADPH. This promotes the generation of reduced glutathione that protects the sulfhydryl groups of hemoglobin, which are susceptible to oxidation by hydrogen peroxide and oxygen radicals. Red blood cells that lack G6PD also have a deficiency of NADPH. (57)

Red blood cells that are G6PD and NADPH deficient are more susceptible to oxidative stress (for example, by reactive oxygen species and hydrogen peroxide). Oxidative stress occurs naturally, but is increased during illnesses, such as infections and diabetic ketoacidosis. Oxidative stress can also follow the ingestion of fresh fava beans (favism), and is an adverse effect of several drugs, for example, the antimalarial drugs primaquine and tafenoquine, the antibacterials dapsone and sulfamethoxazole, the skin cancer drug dabrafenib, and the uric acid lowering drugs pegloticase and rasburicase (9).

Most individuals with G6PD deficiency are asymptomatic, as they have a normal lifespan and may not know they have G6PD deficiency. However, at birth, they may be predisposed to neonatal jaundice, and throughout life, they will be sensitive to oxidizing agents. All individuals with G6PD deficiency should avoid exposure to oxidizing agents when possible, including antimalarial drugs such as tafenoquine and primaquine.

Symptomatic individuals with G6PD deficiency may suffer from episodes of acute hemolytic anemia or CNSHA. The management of hemolytic episodes depends on the severity of hemolysis, with more severe cases requiring blood transfusions. Folic acid and iron may be given to prevent the worsening of anemia in individuals with folate deficiency and to induce formation of new red blood cells (58).

More than 200 genetic variants of the *G6PD* gene have been identified (59). Most known *G6PD* variants are missense, which can also be inherited as haplotypes that are comprised of more than one variant allele (60). Large deletions are rare, and a complete lack of G6PD activity is thought to be fatal in utero.

The normal (wildtype) copy of the *G6PD* gene is known as *G6PD* B, and is found in most individuals of European descent, individuals of Asian descent, and individuals of African descent. Common *G6PD* variants include:

- *G6PD* A (p.Asn126Asp) has normal enzyme activity and is not associated with hemolysis, and is found in up to 30% of individuals of African descent (61)
- *G6PD* A- (p.Asn126Asp with p.Val68Met) is associated with mild to moderate hemolysis, and is found in up to 15% of African-Americans (62). Additional *A-* haplotypes have also been identified, both with the A variant with a second variant (p.Asn126Asp with p.Arg227Leu; and p.Asn126Asp with p.Leu323Pro. See Nomenclature table below for additional information) (63)
- *G6PD* Mediterranean (p.Ser218Phe) can cause severe hemolysis, and is a common pathogenic variant in individuals of European descent (64)
- *G6PD* Canton (p.Arg489Leu) can cause severe hemolysis, and is found in individuals of Asian descent (65)
- *G6PD* Viangchan (p.Val291Met) is the most common *G6PD* variant among Thais, Laotians, Cambodians, and Malaysians (based on common genetic ancestry) (66, 67)

The WHO recently updated its categorization of *G6PD* variants into 4 classes based on the median residual enzyme activity in males (expressed as a percentage of normal activity) (68). Class A variants have <20% activity and are associated with chronic hemolytic anemia. Most individuals with G6PD deficiency have variants that belong to class B (enzyme activity less than 45%). Class B variants are associated with intermittent hemolysis, usually triggered by infection or drugs, but most of the time, affected individuals are asymptomatic. Class C variants show median G6PD activity from 60–150% and are not associated with hemolysis. In class U are the variants with any activity and unknown clinical significance. The CPIC has assigned G6PD phenotypes based on *G6PD* genotypes under the previous classification system (9); the updated WHO categories are also provided (Table 3) (9).

Table 3. Assignment of likely G6PD Phenotype based on Genotype/Diplotype (CPIC, 2022)

Likely phenotype	Definition[a]	Genotype	WHO class for G6PD variants[b]	Example of diplotype[c]
Normal	Very mild or no enzyme deficiency, no less than 60% of normal enzyme levels (60–150% of normal activity)	An X chromosome hemizygote who has a nondeficient (class IV) allele	IV (C)	B, Sao Borja
		An individual who has 2 nondeficient (class IV) alleles	IV/IV (C)	B/B, B/Sao Borja
Deficient	Less than 10–60% of normal enzyme activity (20–45% of normal activity)	An X chromosome hemizygote who has a deficient (class II–III) allele	II, III (B)	A–, Orissa, Kalyan-Kerala, Mediterranean, Canton, Chatham
		An individual who has 2 deficient (class II–III variants) alleles	II/II, II/III, III/III (B)	A–/A–, A–/Orissa, Orissa/Kalyan-Kerala, Mediterranean/Mediterranean, Chatham/Mediterranean, Canton/Viangchan
Deficient with CNSHA	Severe enzyme deficiency (<10% activity) and associated with CNHSA (<20% of normal activity)	An X chromosome hemizygote who has a class I allele	I (A)	Bangkok, Villeurbanne
		An individual who has 2 deficient (class I variants) alleles	I/I (A)	Bangkok/Bangkok, Bangkok/Villeurbanne

Table 3. continued from previous page.

Likely phenotype	Definition[a]	Genotype	WHO class for G6PD variants[b]	Example of diplotype[c]
Variable[d]	Normal or deficient enzyme activity[c]	An individual who has one nondeficient (class IV) and one deficient (class I–III variants) allele	IV/I, IV/II, IV/III (U)	B/A–, B/Mediterranean, B/Bangkok
Indeterminant	Uncertain		(U)	

CNSHA - chronic non-spherocytic hemolytic anemia; WHO - World Health Organization; G6PD - glucose-6-phosphate dehydrogenase; CPIC - Clinical Pharmacogenetics Implementation Consortium

[a] The traditional (Class I-IV) and updated (A, B, C, and U) activity levels are both provided, with the updated activity ranges provided in parentheses where relevant.

[b] WHO classifications were under revision at the time of CPIC publication, updated classification (using A, B, C and U designations) have been proposed based on enzyme activity levels and are provided in parenthesis here (68).
Class I alleles are extremely rare; the distinction between class II and III alleles is not clear. Almost all individuals will have class II, III, or IV alleles. It should be noted that the class of a variant may have been assigned only by the clinical manifestations of an individual in which the variant was subsequently identified.

[c] Due to the large number of G6PD variants, many other diplotypes may be possible besides those given as examples here; see Supplementary data from (9) for a more comprehensive list of alleles with their assigned WHO class. For Human Genome Variation Society terms, please see the Nomenclature table below. The alleles and diplotypes provided here are based upon the historic class I–IV definitions and may not fit the updated WHO classification.

[d] Due to X-linked mosaicism, females heterozygous for one nondeficient (class IV) and one deficient (class I–III variants) allele may display a normal or a deficient phenotype. It is therefore difficult to predict the phenotype of these individuals (Supplementary Material online [G6PD heterozygotes]) (9).
This table is adapted from (9).

Additional Genes of Note

Chloroquine is metabolized by the enzymes encoded by *CYP2C8*, *CYP3A4* and *CYP2D6*, all of which are classified as "very important pharmacogenes" by PharmGKB (69, 70). Variability in the *CYP* genes can lead to reduced or, occasionally, increased enzyme function. Classification of individual phenotypes as either ultrarapid metabolizers, normal metabolizers, intermediate metabolizers, or poor metabolizers is carried out on a predictive basis from genotype/diplotype results of known alleles. Allele definitions for various genes are available from CPIC (71) and the Pharmacogene Variation Consortium (PharmVar) (72), and *CYP2D6* allele functional classifications are also available from CPIC (71) and PharmVar (72). Allele frequencies for these pharmacogenes vary across global and even regional populations (71, 73, 74, 75, 76).

Interaction of chloroquine with these CYP enzymes leads to varying degrees of enzyme inhibition (36). These interactions may decrease the enzymatic function of these CYP proteins relative to any single drug. This results in phenoconversion, a phenomenon where an individual's genetically predicted CYP metabolism is altered to a different activity level. Drugs competing for the same metabolic enzyme will often lead to phenoconversion with lower effective enzyme activity. Studies have found chloroquine administration can inhibit CYP2D6 activity in vitro and in vivo in normal metabolizers and in some cases, this led to phenoconversion to a poor-metabolizer phenotype for primaquine metabolism (77, 78, 79).

Transporter proteins encoded by solute carrier organic anion transporter (*SLCO)* genes, also known as OATPs, adenosine triphosphate (ATP)-binding cassette sub-family B member 1 *(ABCB1)* or P-glycoprotein, ATP-binding cassette sub-family C member 1 (*ABCC1)* or MRP1, and ATP-binding cassette sub-family C member 2 (*ABCC2)* or MRP2 have all been shown to have their function impacted by chloroquine (36).

Sortica and colleagues studied 164 individuals infected with *P. vivax* treated with chloroquine and primaquine and found a significant interaction between variants in *SLCO2B1* (c.935G>A) and treatment over time on the rate of parasite clearance; they further observed an effect from variants in *SLCO1A2* and *SLCO1B1* on

gametocyte clearance over time. Their data suggests that individuals with *SLCO1A2*2* or **3* alleles have a slower clearance rate for gametocytes during antimalarial therapy as compared with **1* homozygous individuals, though this may be due to changes in chloroquine binding, as it is a known substrate for the encoded transporter OATP1A2. The effect from *SLCO1B1* variants (namely the **14* allele) was significant when considered as a change in gametocyte clearance over time. (80)

The ATP-binding cassette (ABC) family of proteins and OATPs are important drug transport proteins and altered function of these enzymes can affect the efficacy of substrate medications and potential side effects. In the case of P-glycoprotein, the effect of chloroquine is weak inhibition of the transport protein and thus is not expected to significantly affect the transporter activity nor chloroquine metabolism. However other substrates may be adversely affected and co-medication with drugs that further inhibit transport may lead to significant effects (36). One study found chloroquine to be a potent inhibitor of the OATP1A2 transport protein, potentially impacting uptake of all-trans-retinol in the retinal pigment epithelium (81).

Linking Gene Variation with Treatment Response

Individuals with G6PD deficiency (less than 60% normal enzyme activity) may be at a higher risk for hemolysis when exposed to chloroquine than those individuals with normal G6PD enzyme activity (1, 63, 82). However, both the CDC and WHO recommend chloroquine prophylaxis to prevent malaria relapse for pregnant and breastfeeding women, as primaquine is contraindicated during pregnancy and in G6PD deficiency (<30% enzymatic activity) (7). The FDA-approved drug label recommends monitoring individuals on prolonged therapy for signs of hemolysis; the recommended test is complete blood counts (1).

Genetic variation in *CYP2C19*, *ABCG2,* and *UGT2B7* leading to decreased enzyme activity—when present with CYP2D6 intermediate- or poor-metabolizer status—may predispose individuals to a higher risk of *P. vivax* relapse for individuals treated with a combination primaquine and chloroquine regimen (83). Individuals with low-activity *CYP2C8* alleles have also been reported to have reduced gametocyte clearance rate as compared with those with normal function alleles (84). These pharmacogenetic effects may be due primarily to the impact on primaquine rather than chloroquine metabolism.

The CYP2D6 enzyme is critical for the metabolism of a large number of drugs and some evidence suggests that chloroquine use can further reduce enzymatic activity in individuals with already reduced CYP2D6 activity (36). Medications such as metoprolol and tamoxifen depend upon CYP2D6 metabolism and may be negatively impacted by co-medication with chloroquine (85, 86). This may lead to altered therapeutic response for all concomitant medications, and increase the risk of retinal damage in the case of tamoxifen co-medication (1).

Transport proteins for chloroquine show some genetic variation that has been associated with differences in malaria response. One study of combination therapy with chloroquine and primaquine found that variants in *SLCO2B1* (encoding OATP2B1), *SLCO1B1* (encoding OATP1B1), and *SLCO1A2* (encoding OATP1A2) were associated with differences in parasite and gametocytemia clearance rates (80).

However, there are no specific actionable guidelines from the pharmacogenetics community or the FDA (1) to alter antimalarial medication based on variation of any the genes discussed herein.

The *G6PD* Gene Interactions with Medications Used for Additional Indications

Medications that can induce oxidative stress in red blood cells can trigger hemolysis readily in individuals with G6PD enzyme deficiency. Antimalarials, such as tafenoquine and primaquine, are one class of medication that often pose a risk for G6PD deficient individuals, but many more medications require special attention to G6PD status.

- Urate-lowering medications: both refractory gout and tumor lysis syndrome can cause systemic elevation of urate levels, medications such as rasburicase and pegloticase are uricase enzymes that aid in the breakdown of uric acid into more soluble metabolites. These reactions produce hydrogen peroxide as a byproduct, thus increasing oxidative stress in the body.
- Anti-microbial medications: nitrofurantoin, often used for urinary tract infections, was determined to be a medication of moderate risk for AHA in G6PD-deficient individuals by CPIC and may call for additional monitoring. In contrast, CPIC found sulfamethoxazole to be a medication with low-to-no risk in G6PD deficient individuals. (9)

Additional information on gene-drug interactions for *G6PD* are available from PharmGKB, CPIC and the FDA (search for "G6PD").

Genetic Testing

The NIH Genetic Testing Registry (GTR) displays genetic tests that are available for chloroquine response and the *G6PD* gene. Molecular genetic testing can be used to confirm the diagnosis of G6PD deficiency and testing may also be used to screen females with a family history of G6PD deficiency to see if they are carriers. In routine clinical practice, G6PD deficiency is diagnosed by measuring G6PD activity in red blood cells (57, 58). Two different types of enzyme activity tests are used, and they are classified as qualitative or quantitative. For some medications, such as tafenoquine, a specific enzymatic activity threshold is used to determine the safety of the medication and as such a quantitative test may be required for individuals with intermediate levels of enzyme activity based on the qualitative test (87). False results may be obtained immediately after a blood transfusion, because transfused cells are likely to have normal G6PD levels, and immediately after an episode of hemolysis, because young red blood cells have higher levels of G6PD. Therefore, when necessary, screening for G6PD enzymatic activity should be performed 2–3 months after a blood transfusion or hemolytic episode (9, 57). Diagnosis using qualitative test methods is less accurate for females with intermediate G6PD activity due to heterozygous *G6PD* alleles (88).

Glucose-6-phosphate dehydrogenase deficiency occurs in homozygous and compound heterozygous individuals (who have inherited 2 copies of *G6PD* deficient alleles) and in heterozygous individuals (one normal *G6PD* allele and one deficient *G6PD* allele) with skewed X chromosome inactivation of the functional allele or in individuals who are hemizygous for a single deficient allele (54). Genetic testing alone is insufficient for heterozygous individuals with one normal function *G6PD* allele, as the expression of the 2 alleles will vary between blood cells and over time (9). Genetic testing for *G6PD* variants may reveal an incidental finding of an unexpected number of *G6PD* alleles based on the apparent gender of the tested individual; these findings may warrant additional consultation or testing.

Glucose-6-phosphate dehydrogenase deficiency is inherited in an X-linked recessive pattern and most individuals are asymptomatic throughout life. A heterozygous mother has a 50% chance of passing G6PD deficiency to a son and a 50% chance of passing the carrier trait to a daughter. Affected fathers pass the variant *G6PD* to their daughters, but not to their sons. X-linked disorders affect males at a much higher rate than females because males only have one copy of the X chromosome (hemizygous, XY). Since females have 2 copies of the X chromosome (XX) they tend to be less affected. However, female carriers can present with a range of phenotypes from no symptoms through a severe deficiency. Females randomly inactivate one X chromosome in somatic cells during development, resulting in a mixed population of somatic cells expressing one *G6PD* allele or the other.

Therapeutic Recommendations based on Genotype

This section contains excerpted [1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2022 Statement from the US Food and Drug Administration (FDA):

Chloroquine may cause hemolysis in glucose-6 phosphate dehydrogenase (G-6-PD) deficiency. Blood monitoring may be needed as hemolytic anemia may occur, in particular in association with other drugs that cause hemolysis.

Please review the complete therapeutic recommendations that are located here: (1)

Nomenclature for Selected *G6PD* Alleles

Common allele name / condition	Alternative names / condition	HGVS reference sequence		WHO Classification*	dbSNP reference identifier for allele location
		Coding	Protein		
G6PD B	WT	NM_001042351.3	NP_001035810.1	IV/ Normal	--
G6PD A+	p.Asn126Asp	NM_001042351.3:c.376A>G	NP_001035810.1:p.Asn126Asp	IV/ Normal	rs1050828
G6PD Sao Borja	p.Asp113Asn	NM_001042351.3:c.337G>A	NP_001035810.1:p.Asp113Asn	IV/ Normal	rs5030870
G6PD A-	A-$^{202A/376G}$	NM_001042351.3:c.376A>G	NP_001035810.1:p.Asn126Asp	III/ Deficient (B)	rs1050828 rs1050829
		NM_001042351.3:c.202G>A	NP_001035810.1:p.Val68Met		
G6PD A-	A-$^{680T/376G}$	NM_001042351.3:c.376A>G	NP_001035810.1:p.Asn126Asp	III/ Deficient	rs1050828 rs137852328
		NM_001042351.3:c.680G>T	NP_001035810.1:p.Arg227Leu		
G6PD A-	A-$^{968C/376G}$	NM_001042351.3:c.376A>G	NP_001035810.1:p.Asn126Asp	III/ Deficient (B)	rs1050828 rs76723693
		NM_001042351.3:c.968T>C	NP_001035810.1:p.Leu323Pro		
G6PD Bangkok	p.Lys275Asn	NM_001042351.3:c.202G>A	NP_001035810.1:p.Val68Met	III/ Deficient (A)	
G6PD Kalyan-Kerala	p.Glu317Lys	NM_001042351.3:c.949G>A	NP_001035810.1:p.Glu317Lys	III/ Deficient (U)	rs137852339
G6PD Orissa	p.Ala44Gly	NM_001042351.3:c.131C>G	NP_001035810.1:p.Ala44Gly	III/ Deficient (B)	rs78478128
GP6D Canton	p.Arg459Leu	NM_001042351.3:c.1376G>T	NP_001035810.1:p.Arg459Leu	II/ Deficient (B)	rs72554665
G6PD Chatham	p.Ala335Thr	NM_001042351.3:c.1003G>A	NP_001035810.1:p.Ala335Thr	II/ Deficient (B)	rs5030869
G6PD Mediterranean	p.Ser188Phe	NM_001042351.3:c.563C>T	NP_001035810.1:pSer188Phe	II/ Deficient (A)	rs5030868
G6PD Viangchan	p.Val291Met	NM_001042351.3:c.871G>A	NP_001035810.1:p.Val291Met	II/ Deficient (B)	rs137852327

[1] *The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug. Certain terms, genes and genetic variants may be corrected in accordance to nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.*

Table continued from previous page.

Common allele name / condition	Alternative names / condition	HGVS reference sequence		WHO Classification*	dbSNP reference identifier for allele location
		Coding	Protein		
G6PD Villeurbanne	p.Thr334del	NM_001042351.3:c.1000_1002delACC	NP_001035810.1:pThr334del	I/Deficient with CNSHA	

Additional allele information available from PharmGKB and CPIC's G6PD Allele Definition Table (revised 2018).
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
* WHO classifications based on (89), classification of these alleles under the updated WHO categories are taken from work described in (90) and the data deposited at (91). Please note that not all alleles have an updated classification at the time of writing.
WHO - World Health Organization; PharmGKB - Pharmacogenomics Knowledgebase; CPIC - Clinical Pharmacogenetics Implementation Consortium; CNSHA - chronic non-spherocytic hemolytic anemia, G6PD - glucose-6-phosphate dehydrogenase

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