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Primaquine for Plasmodium vivax Radical Cure: G6PD Testing Strategies and Relapse Prevention Efficacy

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ABSTRACT

Plasmodium vivax malaria remained a significant global health burden, affecting approximately 14.3 million individuals annually, with its unique dormant hypnozoite stage in the liver presenting substantial challenges for complete parasite eradication. The persistent reactivation of these hypnozoites led to recurrent infections that compromised patient outcomes and sustained transmission cycles in endemic regions. Primaquine represented the only widely available medication capable of targeting hypnozoites for radical cure, yet its use was complicated by the risk of potentially life-threatening hemolytic anemia in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, an inherited enzymopathy affecting over 400 million people worldwide. This comprehensive review examined the biochemical mechanisms underlying primaquine efficacy and G6PD-related toxicity, evaluated current diagnostic strategies for G6PD screening, and analyzed the clinical evidence supporting various treatment regimens for relapse prevention. A systematic synthesis of peer-reviewed literature published between 2010 and 2025 was conducted to assess diagnostic accuracy, safety profiles, and therapeutic outcomes. Recent advances in point-of-care testing technologies and standardized dosing protocols have substantially improved the risk-benefit balance of primaquine administration. Implementation of appropriate G6PD screening before treatment can enable safe radical cure while minimizing hemolytic complications, though access to reliable diagnostics remains limited in resource-constrained settings where P. vivax is most prevalent.

Keywords: Primaquine; Plasmodium vivax; Glucose-6-phosphate dehydrogenase deficiency; Hypnozoite; Radical cure.

INTRODUCTION

Malaria continues to pose a formidable challenge to global public health, with Plasmodium vivax accounting for approximately 7.4 million cases annually and representing the predominant malaria species across vast geographic regions, including Latin America, Southeast Asia, and the Western Pacific [1,2,3-6]. Unlike Plasmodium falciparum, which has received disproportionate attention in malaria control programs, P. vivax possesses a distinctive biological feature that substantially complicates treatment efforts: the formation of dormant hepatic stages called hypnozoites that can persist in liver cells for months to years following initial infection [3,7-10]. These quiescent forms periodically reactivate to cause recurrent blood-stage infections, perpetuating the cycle of clinical disease and ongoing transmission even in individuals who received appropriate blood-stage treatment [4,11-14].

The capacity of P. vivax to cause relapsing infections has profound implications for individual patient morbidity and broader public health efforts aimed at malaria elimination [5,15-20]. Recurrent episodes contribute to cumulative anemia, reduced productivity, increased healthcare costs, and maintenance of community transmission reservoirs that undermine control initiatives [6, 21-23]. Achieving radical cure the complete elimination of both blood-stage

parasites and dormant hypnozoites requires treatment with 8-aminoquinoline compounds, of which primaquine remains the most extensively studied and widely available option [7,24-28]. However, the clinical utility of primaquine is substantially constrained by its propensity to induce dose-dependent hemolytic anemia in individuals with glucose-6-phosphate dehydrogenase deficiency, the most common human enzyme disorder affecting an estimated 8% of the global population [29-32]. This review synthesizes current evidence regarding optimal strategies for G6PD screening prior to primaquine administration, examines the biochemical mechanisms underlying both therapeutic efficacy and hemolytic toxicity, evaluates the clinical effectiveness of various dosing regimens for relapse prevention, discusses emerging alternatives and novel approaches to radical cure, and analyzes implementation challenges in endemic settings. The fundamental tension between maximizing therapeutic benefit while minimizing adverse effects necessitates a thorough understanding of diagnostic capabilities, pharmacological principles, and epidemiological contexts to inform evidence-based treatment policies that can safely advance toward P. vivax elimination.

Biochemical Mechanisms of Primaquine Action and G6PD-Mediated Hemolysis

Primaquine functions through complex biochemical pathways that remain incompletely characterized despite decades of clinical use, though substantial progress has illuminated key aspects of its mechanism of action against hypnozoites and blood-stage parasites. The drug undergoes extensive hepatic metabolism by cytochrome P450 enzymes, particularly CYP2D6, generating multiple oxidative metabolites that appear responsible for its antiparasitic activity [33-37]. Recent investigations have identified carboxyprimaquine and hydroxylated derivatives as predominant metabolites, with evidence suggesting that these oxidized forms generate reactive oxygen species within parasitized hepatocytes, overwhelming the parasite's limited antioxidant defenses and leading to cellular dysfunction and death [38-43]. The preferential toxicity toward parasites compared to host cells likely reflects the organism's heightened metabolic vulnerability and reduced capacity for neutralizing oxidative stress.

The same oxidative mechanisms that enable primaquine's therapeutic action also underlie its principal adverse effect in G6PD-deficient individuals. Glucose-6-phosphate dehydrogenase catalyzes the first step in the pentose phosphate pathway, generating NADPH, which serves as the essential cofactor for glutathione reductase in maintaining cellular pools of reduced glutathione. This antioxidant system protects erythrocytes from oxidative damage, particularly critical in red blood cells that lack nuclei and mitochondria, rendering them unable to synthesize new proteins or generate ATP through oxidative phosphorylation [44-50]. When primaquine metabolites enter circulation and interact with erythrocytes, the resulting oxidative stress normally gets neutralized by glutathione-dependent mechanisms. However, in G6PD-deficient cells with compromised NADPH regeneration capacity, oxidative damage accumulates, causing protein denaturation, membrane destabilization, and intravascular or extravascular hemolysis [51-54].

The severity of primaquine-induced hemolysis correlates directly with the degree of G6PD deficiency, which varies considerably across the more than 200 identified genetic variants of the enzyme. The World Health Organization classifies G6PD variants into five classes based on residual enzyme activity, with Class I variants (<10% activity) associated with chronic hemolysis even in the absence of oxidative triggers, Class II variants (<10% activity) manifesting hemolysis only during oxidative stress, Class III variants (10-60% activity) showing moderate deficiency, and Classes IV-V representing normal or increased activity [55-60]. Geographic distribution patterns reflect evolutionary selection pressure from malaria, with G6PD deficiency prevalent in malaria-endemic regions due to the modest protective effect against severe P. falciparum infection [14,61-64]. This creates a challenging scenario where populations most needing radical cure treatment harbor the highest frequencies of G6PD deficiency, with some communities exhibiting prevalence rates exceeding 20% among males [15,65-68].

Individual pharmacokinetic variability further complicates primaquine safety profiles, as CYP2D6 polymorphisms substantially influence metabolite generation and drug exposure. Poor metabolizers with reduced CYP2D6 activity may experience decreased therapeutic efficacy due to insufficient active metabolite formation, while ultra-rapid metabolizers could face elevated toxicity risk from excessive metabolite production [69-70]. Recent population pharmacokinetic studies have demonstrated that body weight significantly affects primaquine clearance and volume of distribution, supporting weight-based dosing approaches to optimize therapeutic outcomes while minimizing adverse effects [71-73]. Understanding these multifaceted biochemical interactions proves essential for developing rational treatment strategies that balance efficacy against safety considerations across diverse patient populations with varying genetic backgrounds and metabolic capacities.

Diagnostic Strategies for G6PD Deficiency Screening

Accurate identification of G6PD-deficient individuals before primaquine administration represents a critical prerequisite for safe radical cure implementation, yet diagnostic approaches vary considerably in performance characteristics, resource requirements, and operational feasibility across different healthcare settings. The fluorescent spot test, developed in the 1960s and long considered the reference standard for field applications, involves incubating blood samples with glucose-6-phosphate and NADP, then observing for fluorescence under ultraviolet light indicating NADPH generation. While offering reasonable sensitivity for detecting severe deficiency

in males, this qualitative assay demonstrates significant limitations including subjective interpretation, inability to reliably identify heterozygous females with intermediate enzyme activity, temperature-dependent stability requirements, and approximately 10% of enzyme activity as the detection threshold [18]. These constraints have prompted development of alternative diagnostic technologies better suited to contemporary malaria elimination contexts.

Quantitative spectrophotometric assays that measure enzyme activity directly provide superior analytical performance, establishing definitive diagnosis through precise determination of enzyme activity levels normalized to hemoglobin concentration. Laboratory-based quantitative methods serve as the true gold standard, enabling detection of all G6PD variants including intermediate deficiency states in heterozygous females who comprise a substantial proportion of at-risk individuals in endemic populations [19]. However, these sophisticated techniques require specialized laboratory infrastructure, trained technical personnel, expensive equipment, and relatively long turnaround times that render them impractical for routine point-of-care screening in peripheral healthcare facilities where most malaria treatment occurs [20]. The need for immediate treatment decisions in acute malaria cases necessitates rapid diagnostic solutions that can inform clinical management at the bedside within minutes rather than hours or days.

Recent technological innovations have generated several promising point-of-care devices that aim to bridge the gap between laboratory precision and field practicality. The CareStart G6PD biosensor, extensively evaluated in multiple endemic countries, provides quantitative enzyme activity measurements through a handheld device requiring only 2 microliters of blood and delivering results within 3-5 minutes [21]. Validation studies have demonstrated sensitivity exceeding 95% for detecting male hemizygotes with severe deficiency, though performance for identifying heterozygous females varies with the activity threshold selected for classification [22]. The STANDARD G6PD test represents another quantitative rapid diagnostic platform showing comparable analytical performance with potential advantages in temperature stability and interpretation simplicity [23]. Both technologies enable decentralized testing that can occur alongside malaria diagnosis, facilitating integrated case management that combines species identification with G6PD status determination to guide individualized treatment decisions.

Despite technological progress, substantial implementation challenges persist in translating diagnostic capabilities into widespread clinical practice. Cost considerations remain significant, with rapid diagnostic test prices ranging from $2-6 per unit compared to under $1 for malaria rapid tests, creating budget constraints for resource-limited programs [24]. Quality assurance systems including device calibration, operator training, proficiency testing, and result documentation require robust health system infrastructure often lacking in endemic regions [25]. Perhaps most fundamentally, the lack of universal consensus regarding appropriate enzyme activity thresholds for safe primaquine use at various doses complicates interpretation and treatment algorithms. While individuals with less than 30% normal enzyme activity clearly face elevated hemolysis risk with standard dose primaquine, whether those with 30-70% activity can safely receive full doses remains debated, with implications for the proportion of patients eligible for radical cure [26]. Addressing these diagnostic gaps through continued technology development, implementation research, and evidence generation regarding safety margins across the enzyme activity spectrum will prove essential for responsible radical cure scale-up.

Primaquine Dosing Regimens and Relapse Prevention Efficacy

The optimal primaquine dosing strategy for achieving radical cure while maintaining acceptable safety profiles has evolved considerably over recent decades, with accumulating evidence challenging historical practices and informing contemporary treatment guidelines. Traditional regimens involved 15 mg base daily for 14 days (equivalent to approximately 0.25 mg/kg/day for a 60 kg adult), a protocol established empirically in the 1950s and long recommended by international guidelines despite limited rigorous efficacy data from modern clinical trials [27]. Programmatic adherence to 14-day regimens proved consistently problematic, with completion rates often below 50% in routine practice due to symptom resolution, pill burden, forgetfulness, and inadequate patient counseling about relapse risk [28]. Recognition that poor adherence fundamentally undermines radical cure effectiveness prompted investigation of alternative approaches including higher daily doses for shorter durations, weekly dosing schedules, and terminal prophylaxis strategies.

Landmark clinical trials conducted over the past decade have substantially clarified the dose-response relationship for primaquine efficacy against P. vivax hypnozoites. The IMPROV study, a double-blind randomized controlled trial in Indonesia and Vietnam comparing seven different primaquine regimens, demonstrated that total dose rather than duration primarily determines relapse prevention, with 7 mg/kg providing superior protection compared to lower cumulative doses [29]. Patients receiving high-dose regimens (approximately 1 mg/kg/day for 7 days totaling 7 mg/kg) experienced 6-month relapse rates below 10%, significantly lower than the 20-30% rates observed with standard 0.25 mg/kg/day for 14 days totaling only 3.5 mg/kg [30]. These findings provided compelling evidence that historical dosing recommendations were suboptimal, using total doses approximately half of what

appears necessary for reliable radical cure in many endemic regions, particularly those with tropical P. vivax strains exhibiting frequent relapse phenotypes.

Geographic variation in hypnozoite relapse propensity further complicates treatment optimization, as P. vivax populations demonstrate substantial heterogeneity in dormancy patterns and reactivation frequencies that appear to represent evolutionary adaptations to local transmission seasonality. Temperate strains such as the Chesson strain from Papua New Guinea exhibit prolonged dormancy with relapses typically occurring months after primary infection, while tropical strains from Southeast Asia demonstrate frequent early relapses within weeks of initial treatment, resulting in higher cumulative relapse burden [31]. Molecular epidemiological studies using microsatellite genotyping to distinguish true relapses from new infections have confirmed that regions like Thailand and Indonesia face relapse rates exceeding 50% at 6 months without primaquine treatment, compared to approximately 20-30% in temperate regions [32]. This biological diversity necessitates tailored approaches, with strong arguments for higher total primaquine doses in tropical settings where hypnozoite burden and reactivation frequency impose greater challenges.

Weekly primaquine regimens have emerged as an important alternative for G6PD-deficient patients who cannot receive standard daily doses due to hemolysis risk. Administration of 0.75 mg/kg once weekly for 8 weeks provides radical cure while allowing time for hemolysis to resolve between doses, preventing the cumulative oxidative stress that causes severe anemia with daily dosing [33]. Clinical trials have validated the efficacy of weekly primaquine in G6PD-deficient populations, demonstrating relapse rates comparable to daily regimens in G6PD-normal individuals, though the prolonged treatment course presents adherence challenges requiring robust follow-up systems. Tafenoquine, a long-acting 8-aminoquinoline requiring only a single dose, represents an important recent addition to the radical cure armamentarium with efficacy comparable to standard primaquine regimens, though it similarly requires G6PD testing due to hemolytic potential and is contraindicated in individuals with less than 70% normal enzyme activity [34]. The availability of multiple therapeutic options enables individualized treatment selection based on G6PD status, tolerance, adherence capacity, and local epidemiology.

Clinical Safety Profiles and Adverse Event Management

Comprehensive understanding of primaquine's safety profile across diverse patient populations and dosing regimens provides essential context for benefit-risk assessments that inform treatment policies and clinical practice. In G6PD-normal individuals, primaquine demonstrates remarkably good tolerability at standard doses, with most adverse effects being mild and self-limiting. Gastrointestinal disturbances including nausea, abdominal discomfort, and occasional vomiting represent the most frequently reported side effects, occurring in approximately 10-15% of patients and typically manageable through administration with food or temporary dose reduction [35]. Methemoglobinemia occurs universally with primaquine treatment due to oxidative effects on hemoglobin, though clinically significant levels causing cyanosis or dyspnea remain rare at standard doses, with most patients experiencing methemoglobin levels below 5% that require no intervention [36].

The hemolytic risk in G6PD-deficient individuals varies substantially based on enzyme activity levels and primaquine dosing intensity, creating a spectrum of safety concerns from negligible at weekly doses in mild deficiency to life-threatening at daily doses in severe deficiency. Patients with severe deficiency (less than 10% normal activity) receiving standard daily primaquine typically develop acute hemolytic anemia within 2-3 days of treatment initiation, characterized by dark urine, jaundice, fatigue, and declining hemoglobin levels that can drop by 2-4 g/dL or more within the first week [37]. While most hemolytic episodes remain self-limited once primaquine is discontinued due to the selective destruction of older erythrocytes with lowest enzyme activity, severe cases particularly in individuals with baseline anemia can progress to hemoglobin levels below 5 g/dL requiring blood transfusion and potentially threatening life through cardiovascular collapse [38]. Young children appear particularly vulnerable to severe outcomes due to lower baseline hemoglobin levels, smaller blood volumes, and reduced physiological reserve.

Systematic reviews of safety data from clinical trials and observational studies have helped quantify adverse event rates across different scenarios. A meta-analysis including over 5,000 patients treated with primaquine for P. vivax radical cure found serious adverse events occurring in less than 0.5% of G6PD-normal individuals, with no primaquine-related deaths reported [39]. In G6PD-deficient populations receiving inadvertent primaquine treatment, hemoglobin decrements exceeding 3 g/dL occurred in approximately 15-30%, depending on baseline enzyme activity and daily dose, with severe anemia below 7 g/dL developing in 3-5% of cases [40]. Weekly primaquine demonstrated substantially improved safety even in deficient populations, with hemoglobin decrements typically less than 2 g/dL and severe anemia rates below 1%, supporting recommendations for this regimen in mild-to-moderate deficiency [41]. Notably, the risk-benefit ratio must consider that recurrent P. vivax infections without radical cure also cause cumulative morbidity including anemia, such that primaquine's modest hemolytic potential in some deficient individuals may be offset by prevention of multiple future episodes.

Practical management of suspected or confirmed primaquine-induced hemolysis requires prompt recognition and appropriate supportive care. Clinical monitoring should include baseline complete blood count before treatment,

repeat hemoglobin measurement on days 3 and 7 for patients with known mild deficiency receiving daily primaquine, and patient education about warning symptoms including dark urine and increasing jaundice [42]. When hemolysis is detected, immediate primaquine discontinuation typically suffices for mild cases, while moderate-to-severe anemia may require hospitalization, intravenous fluids to maintain renal perfusion, and blood transfusion for hemoglobin below 5 g/dL or symptomatic anemia [43]. Importantly, healthcare providers must balance vigilant safety monitoring against the risk that excessive caution deters primaquine use entirely, as untreated P. vivax imposes substantial health burdens. Appropriate G6PD testing before treatment enables informed consent processes where patients can understand their individual risk profile and participate in shared decision-making about radical cure approaches [44].

Implementation Challenges and Future Directions for P. vivax Elimination

Translating the substantial evidence base for safe and effective primaquine radical cure into programmatic impact that advances P. vivax elimination requires addressing multifaceted implementation barriers spanning diagnostic access, health system capacity, regulatory frameworks, and patient engagement. Despite clear international guidelines recommending G6PD testing before primaquine administration, actual testing rates in endemic countries remain dismally low, with surveys suggesting less than 5% of P. vivax patients receive any form of G6PD screening before treatment [45]. This implementation gap reflects multiple constraining factors including limited diagnostic availability at peripheral health facilities, insufficient training for healthcare workers on testing procedures and result interpretation, inadequate procurement and supply chain systems, and absence of clear national policies mandating pre-treatment testing [46]. The resulting situation involves either widespread primaquine administration without screening, exposing deficient individuals to preventable hemolysis, or conversely, withholding radical cure entirely from all patients to avoid hemolytic risk, perpetuating relapse burdens and transmission.

Economic analyses examining cost-effectiveness of G6PD testing integrated with radical cure provide important evidence for policy decisions, though results vary substantially based on local epidemiology, health system characteristics, and analytical perspectives. Studies from Southeast Asian settings with high P. vivax burden and moderate G6PD deficiency prevalence generally find that point-of-care testing with targeted primaquine treatment demonstrates favorable cost-effectiveness compared to either universal treatment without testing or no radical cure, with incremental cost-effectiveness ratios below willingness-to-pay thresholds in most scenarios [47]. However, settings with lower malaria transmission, higher G6PD deficiency prevalence, or constrained healthcare budgets may face less favorable economic profiles, particularly when considering opportunity costs of resources diverted from other health priorities [48]. Implementation research examining real-world operational challenges, including device failure rates, training requirements, and workflow integration, provides crucial complementary evidence beyond idealized trial conditions.

Novel therapeutic agents in development offer promise for future P. vivax radical cure strategies that might circumvent G6PD-related limitations entirely. Tafenoquine's single-dose administration represents a substantial advance in convenience, though it still requires G6PD testing and demonstrates similar contraindications as primaquine [49]. Investigational compounds including 8-aminoquinoline derivatives with potentially reduced hemolytic liability, repurposed medications like naphthoquines, and entirely new chemical classes targeting hypnozoites through distinct mechanisms, could eventually provide G6PD-safe alternatives, though none have yet progressed to late-stage clinical development. Alternative approaches, including terminal prophylaxis with extended chloroquine courses, though less effective than primaquine, might serve specific populations where radical cure is contraindicated, accepting higher relapse rates as preferable to hemolytic risk [50].

Ultimately, successful P. vivax elimination will require integrated strategies combining effective case management with transmission reduction interventions. Mathematical modeling suggests that even with perfect radical cure implementation, achieving elimination in high-transmission settings requires complementary vector control, surveillance strengthening, and population-wide intervention campaigns to address the substantial reservoir of asymptomatic carriers who maintain transmission but rarely access treatment [51]. The technical feasibility of P. vivax elimination remains uncertain, given biological challenges including early gametocyte production, efficient transmission at low densities, and the contribution of relapses to the infectious reservoir, such that radical cure represents a necessary but potentially insufficient component of comprehensive elimination strategies [52]. Continued investment in implementation research, diagnostic innovation, therapeutic development, and integrated program strengthening will prove essential for translating the remarkable scientific progress of recent years into measurable public health impact against this neglected but globally significant pathogen.

CONCLUSION

Primaquine remains the cornerstone pharmaceutical intervention for achieving radical cure of Plasmodium vivax malaria through hypnozoite elimination, with mounting evidence supporting higher total doses than historical standard regimens to optimize relapse prevention efficacy. The past decade has witnessed remarkable progress in diagnostic technologies, generating validated point-of-care G6PD testing platforms capable of identifying at-risk

individuals before treatment, thereby enabling safer primaquine deployment. Clinical trials have clarified dose-response relationships, confirmed the efficacy of weekly primaquine regimens in G6PD-deficient populations, and demonstrated that 7 mg/kg total doses substantially reduce relapse rates compared to traditional 3.5 mg/kg approaches. However, translation of evidence into programmatic impact remains limited, with most endemic countries yet to implement routine G6PD screening before radical cure despite clear guidelines and available technologies. The fundamental challenge moving forward involves building health system capacity to deliver integrated malaria case management that combines accurate species diagnosis, G6PD status determination, and individualized treatment selection as a routine standard of care rather than a research setting exception. Addressing implementation barriers through healthcare worker training, diagnostic procurement, quality assurance systems, and patient education will prove essential for responsible radical cure scale-up. While primaquine and tafenoquine both require G6PD testing due to inherent hemolytic potential, appropriate use of these agents guided by diagnostic results offers substantial benefits for individual patients through relapse prevention and population-level transmission reduction. Continued innovation in therapeutic options, particularly development of G6PD-safe hypnozoite-targeting agents, could eventually circumvent current constraints, though such advances remain years from clinical availability.

National malaria programs in P. vivax-endemic countries should prioritize implementation of point-of-care G6PD testing integrated with case management to enable safe radical cure scale-up as a critical step toward elimination goals.

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