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Plasmodium vivax treatments: what are we looking for?

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Abstract

Purpose of Review—For over 50 years the treatment of *Plasmodium vivax* has relied on a combination of chloroquine plus primaquine, but this strategy is under threat. Chloroquine efficacy is now compromised across much of the vivax endemic world and there are significant operational difficulties in deploying primaquine. We review the recent advances in *P. vivax* chemotherapy that may influence the future management of this neglected pathogen.

Recent Findings—New generation artemisinin combination therapies (ACTs) have shown potent efficacy against the erythrocytic stages of both drug resistant *P. vivax* and *P. falciparum*. Antimalarial regimens containing slowly-eliminated drugs provide a measure of protection against the first, and possibly second, relapse of tropical strains of *P. vivax,* but reliable radical cure is needed to prevent future relapses. Primaquine is currently the only licensed hypnozoitocidal treatment, but requires long treatment courses and its effectiveness in different endemic settings remains largely unknown.

Summary—In regions coendemic for *P. vivax* and *P. falciparum*, a unified treatment policy for malaria of any parasitological cause is likely to confer the greatest individual and public health benefit. Optimizing the safety and effectiveness of primaquine through the development of rapid diagnostic tests for G6PD deficiency and improving drug adherence will be crucial endeavours in the fight against vivax malaria.

Keywords

P. vivax; malaria; drug resistance; antimalarials; primaquine

Introduction

For many centuries vivax malaria has been referred to as ‘benign tertian fever’ because of its 48 hour blood-stage periodicity and perceived lack of life-threatening complications. In the early part of the 20th century, treatment of vivax malaria was reliant on quinine. A major

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“The treatment of *P. vivax*”

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drug discovery program in the 1930s resulted in the identification and development of a variety of potent alternative antimalarials, including the aminoquinoline and antifolate drugs. The Second World War accelerated further drug development driven by the need to deploy military personnel in malarious countries. By the 1950s, chloroquine was established as the preferred blood schizontocidal treatment for *P. vivax* malaria, with primaquine coadministered to prevent relapses from dormant liver stages of the parasite. The combination of chloroquine plus primaquine has remained the default option for treating vivax malaria for almost 50 years. During this period, malaria researchers and policymakers have focused their efforts on tackling the burden of *P. falciparum*, the major cause of global malaria mortality. In the shadow of *P. falciparum,* the development of drugs, diagnostics, and vaccines for *P. vivax* stalled (1).

The last decade has seen a widespread scale-up of insecticide-treated bed nets and highly effective artemisinin combination therapies (ACTs) for uncomplicated falciparum infections. In many places these interventions have been associated with significant reductions in the overall burden of malaria (2, 3). Outside of Africa, where *Plasmodium falciparum* and *P. vivax* invariably co-exist (4), intensive control measures have had a disproportionately greater impact on *P. falciparum* than *P. vivax* (5-7). The control and elimination of *P. vivax* will be far harder than for *P. falciparum.* The comparative refractoriness of *P. vivax* to current malaria control interventions is largely attributed to its dormant liver stages (hypnozoites) which cause recurrent blood stage infections (relapses) weeks-months after initial infection, sustaining transmission, even in environments that are hostile to the mosquito vector for much of the year.

Recent estimates suggest that 40% of the world's population is at risk of *P. vivax* transmission (8) with between 70 and 390 million clinical episodes of vivax malaria each year (9, 10). The net annual cost of those infections has been estimated to be between US $1.4 and 4 billion (10). Although undoubtedly less pathogenic than *P. falciparum, P. vivax* infections have been associated with severe and fatal disease (11-13) and substantial morbidity, particularly severe anemia (14, 15). The socioeconomic consequences of vivax malaria are poorly quantified, but likely to be substantial. (10, 16-18).

In this article we review the antimalarial drug treatments available for *P. vivax* malaria as well as progress in developing new therapeutic options for its control and ultimate elimination (Table 1). Two main aspects of treatment are addressed: removal of erythrocytic parasitemia, and terminal elimination of exoerythocytic hypnozoite stages.

Treatment of P. vivax Erythrocytic Stages

The interpretation of clinical studies for relapsing malarias is challenging (14, 19). Recurrent parasitemia following initial treatment can arise from reinfection, relapse from hypnozoite stages or true recrudescence due to parasite resistance or partial / inadequate therapy. Molecular analysis, which has been so important in confirming true recrudescence in clinical trials of *P. falciparum*, is less helpful in *P. vivax* studies, since it is currently not possible to distinguish between recrudescence and relapse of the same parasite strain. Pharmacokinetic analysis can help to confirm adequate drug absorption and establish whether recurrent infections occur in the face of blood concentrations known to exceed the minimum inhibitory concentration (MIC) of the parasite. Such analyses are often omitted due to logistical constraints or cost. Most of the available antimalarial drugs recommended for asexual treatment are potent schizontocides but have no activity against hypnozoites, hence the timing and recurrence of parasitemia is primarily a function of the elimination half-life of the initial drug treatment rather than its intrinsic schizontocidal activity.

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In clinical trials, antirelapse therapy with primaquine is often administered concomitantly with the schizonticidal study drug. Since the primaquine has both hypnozoitocidal and schizontocidal activity its early administration can augment initial asexual parasite clearance and thus mask early indicators of declining schizontocidal drug efficacy. Vivax malaria drug trials therefore need to be interpreted in light of the concomitant use of primaquine, the timing of recurrence, available molecular data, schizontocidal drug concentrations, entomological inoculation rates and the epidemiology of relapse in the study area.

Chloroquine

Chloroquine (25mg base/kg over three days) remains the treatment of choice for *P. vivax* malaria in most parts of the world due to its wide availability, familiarity amongst health care staff, low cost, potency against sensitive strains (20) and long terminal elimination half-life. However this default option has become increasingly untenable because of the emergence and spread of chloroquine resistant (CQR) strains of the parasite. Despite the aforementioned difficulties in clinical trial interpretation there is now good evidence that the efficacy of chloroquine against *P. vivax* is declining in most locations where vivax malaria is endemic (14, 21). The epicentre of *P. vivax* chloroquine resistance appears to be the island of New Guinea where chloroquine resistance was first discovered and where the majority of individuals with *P. vivax* infection now fail chloroquine therapy (22-25). Recent reports have provided evidence of declining chloroquine efficacy against *P. vivax* from Ethiopia (26, 27), Madagascar (28), India (29), Indonesia (Alor and Lampung), (30, 31), South Korea (32), Myanmar *(33)* and Thailand (34, 35).

Alternative Monotherapies for P. vivax

Most commonly used antimalarial drugs are active against the asexual stages of *P. vivax;* the exception being the antifolates which act slowly (36) and are vulnerable to the rapid development of drug resistance (37, 38). A range of antimalarial drugs have demonstrated good efficacy against chloroquine-resistant *P. vivax* in clinical trials including mefloquine (39), atovaquone+proguanil (40), halofantrine (41), piperaquine (42, 43), artesunate (42, 43), and pyronaridine (44). The activity of these drugs against CQR *P. vivax* has also been confirmed by *in vitro* studies (45, 46). *In vitro* and *in vivo* studies suggest a degree of cross-resistance between chloroquine and amodiaquine (47), and this is likely to have accounted for high recurrence rates in clinical studies from Papua, Indonesia (48) and Papua New Guinea (43).

Artemisinin Combination Therapy for P. vivax Infection

Highly effective artemisinin combination therapies (ACTs) have become the treatment of choice for uncomplicated falciparum malaria, which by 2009 had been adopted by 81 malarious countries as first-line policy (49). Although World Health Organization (WHO) guidelines acknowledge that ACT plus primaquine is an appropriate alternative to chloroquine in regions where chloroquine efficacy is declining (20), there has been limited enthusiasm for such a policy with only The Solomon Islands, Vanuatu, Papua New Guinea (PNG) and Indonesia having adopted ACTs for first-line treatment of vivax malaria by 2009 (49). In general this reflects a lingering perception that ACT is an unnecessary and expensive choice for a disease which can be readily treated in most areas with chloroquine (50). Additional concerns have also been raised regarding the lack of substantial evidence confirming the efficacy of antirelapse regimens when primaquine is administered with schizontocidal drugs other than chloroquine or quinine (51). Despite these caveats there is a growing opinion advocating a unified ACT-based therapy for both *P. falciparum* and *P. vivax* in all coendemic regions. As the cost of ACTs falls and their availability increases the advantages of a pragmatic, unified ACT-based treatment protocol for both *P. falciparum* and *P. vivax* in all co-endemic regions, becomes compelling (21).

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To date there have been 13 published studies of the efficacy of ACT for treating *P. vivax* monoinfection, including assessments of dihydroartemisinin+piperaquine (DHA+PIP) (42, 43, 48, 52-55), artemether+lumefantrine (AM+LUM) (26, 42, 43, 56, 57), artesunate +amodiaquine (AS+AQ) (48), artesunate+sulfadoxine+pyrimethamine (AS+SP) (38, 43, 58) and pyronaridine with either dihydroartemisinin (59) or artesunate (44). Five of these studies come from the island of New Guinea and all but one of the remaining from other parts of Asia.

In all of these studies parasite clearance was rapid (60), indicative of the potent activity of the artemisinins against all asexual stages of *P. vivax* (37). However the rates of recurrence within 28-42 days of ACT administration varied considerably. The risk of recurrent parasitemia was greatest in patients treated with artesunate+sulfadoxine+pyrimethamine (67%) (43), artesunate+amodiaquine (48%) (48) and artemether+lumefantrine (57-70%) (42, 43). In the case of AS+SP and AS+AQ this is likely to reflect compromised efficacy of the slowly-eliminated partner drug. In contrast, high rates of treatment failure with AM+LUM are likely to reflect relapsing infections rather than recrudescent infections; as suggested by 2.6% of Thai patients having recurrent parasitaemia following AM+LUM plus primaquine (57) compared to 57-70% of Papuan patients when primaquine was delayed until the end of the study (42, 43).

The Role of Post Treatment Prophylaxis

None of the current ACTs have any efficacy against the hypnozoite stages of *P. vivax.* Slowly-eliminated drugs, such as piperaquine (half-life ~28 days) and mefloquine (~12 days), provide a clinically significant period of post-treatment prophylaxis (PTP) against blood-stage parasitemia. The duration of this effect depends on the pharmacokinetic profile of the drug, the total dose administered, and the drug susceptibility of the infecting parasites (61). Post-treatment prophylaxis prevents or delays parasite recurrence arising from either new infections (reinfection) or reactivation of dormant liver stages (relapse). The greater the risk of recurrence, the more apparent this prophylactic effect is likely to become. Although transmission intensity tends to be low in most vivax endemic regions, each inoculation with *P. vivax* has the potential to cause multiple future relapses. The number of relapses can vary considerably. In equatorial regions, 60-90% of patients have recurrent *P. vivax* malaria within 42 days of the initial infection (more likely to be relapse rather than reinfection) (43, 48, 62). Such rates of recurrence are comparable to *P. falciparum* reinfections in high transmission settings in Africa (63).

The delay in relapse and reinfections conferred by the use of slowly-eliminated antimalarial drugs for *P. vivax* provides a longer period free from symptomatic malaria, allowing a greater length of time for haematological recovery which in turn reduces the risk of anaemia (42, 48). Reducing recurrent *P. vivax* infections may also impact upon transmission potential to the mosquito vector by decreasing overall gametocyte carriage (34). The risk of relapse and benefits of PTP are not restricted to patients with acute *P. vivax* monoinfection. In regions co-endemic for *P. vivax* and *P. falciparum* the treatment of pure falciparum malaria is followed by *P. vivax* parasitemia in over half of all patients treated with a rapidly-eliminated antimalarial drug by 9 weeks of follow-up (62). Similar to the treatment of *P. vivax* monoinfections, the use of slowly-eliminated antimalarials such as mefloquine or piperaquine reduces markedly the risk of these early heterologous relapses (43, 62, 64-66).

The long-term benefits of prolonged post-exposure prophylaxis are unclear. A single *P. vivax* sporozoite infection can prime the liver with multiple hypnozoites. Although slowly eliminated antimalarials will suppress the first, and possibly the second, relapse in equatorial regions, it remains to be shown whether this will reduce the total number of relapses or

simply delay the occurrence of the next one. If the total number of relapses can be reduced then the PTP will impact upon gametocyte carriage and hence transmissibility.

Severe Vivax Malaria

Severe and fatal vivax malaria has been reported from Indonesia (11, 13), Papua New Guinea (67), India (68) and Brazil (69, 70). The main manifestations are anemia and respiratory distress (13, 67, 71-73). Series of patients with coma, shock and renal and hepatic dysfunction associated with vivax malaria have been described, but may be confounded by comorbidities (68-70, 74). In the absence of comparative drug trials, physicians have tended to adopt a similar treatment approach for severe vivax malaria as for severe falciparum malaria (20), namely administration of parenteral quinine or artesunate, along with broad spectrum antibiotic cover and supportive care.

The SEAQUAMAT and AQUAMAT studies have demonstrated clear superiority of intravenous artesunate over quinine in reducing case-fatality in severe falciparum malaria (75, 76). Intravenous artesunate also leads to a rapid clinical response in patients with severe vivax malaria (13, 74), but there have been no clinical trials comparing the mortality of intravenous artesunate versus quinine for severe *P. vivax* infection. *P. vivax* has a lower infecting parasite biomass compared with *P. falciparum* and does not cause major red blood cell sequestration in the deep vasculature, hence superior efficacy of artesunate over quinine cannot be assumed. Several studies have suggested artemisinin derivatives may result in haematopoietic suppression (77, 78). Since severe anaemia accounts for the greatest proportion of severe manifestations in vivax malaria, it will be important to ensure that artesunate is at least as efficacious as quinine in reducing mortality in severely anaemic patients, as was shown to be the case in children with severe anaemia due to falciparum malaria (76). However given the importance of initiating highly effective schizontocidal treatment as quickly as possible in severe falciparum malaria, the magnitude of the benefit of artesunate compared to quinine in severe falciparum malaria and the difficulties of discriminating between *P. vivax* and *P. falciparum*, a unified policy of intravenous artesunate seems pragmatic and appropriate, although further clinical studies are warranted.

Treatment of P. vivax Exoerythrocytic Stages

Relapsing infections from the exoerythrocytic liver stages are the most important impediment to the success of *P. vivax* control programmes (21, 79). Hypnozoites are insensitive to most schizontocidal drugs and even to agents that are active against liver stage schizonts such as atovaquone+proguanil. Hypnozoites are sensitive to 8-aminoquinoline antimalarial drugs at nanomolar concentrations, although only primaquine is currently licensed (80). Two other 8-aminoquinolines, bulaquine and tafenoquine, are in clinical development (81, 82), but there are very few other hypnozoitocidal candidates from other classes of compounds (83).

The World Health Organization recommends a dose of 0.25-0.5mg/kg primaquine daily for 14 days for radical cure of vivax malaria (20). Primaquine can cause upper gastrointestinal discomfort and life-threatening hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient individuals. In the most recent WHO malaria treatment guidelines primaquine is reported to be contraindicated in children <4 years of age and pregnant women (20) (page 52), the patient groups at greatest risk of morbidity associated with recurrent vivax infections. The risk-benefit of primaquine is unclear especially in young children, where a paucity of safety data rather than overt toxicity, is quoted as a rationale for withholding antirelapse therapy. In practice national malaria control programs often advocate deployment of 14 days primaquine in children as young as one year old, but studies are

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urgently needed to demonstrate primaquine safety in children particularly in infants, and those with mild and moderate G6PD deficiency.

There are as yet no reliable bedside tests for G6PD deficiency. Many health care providers therefore elect to administer primaquine without G6PD testing or simply adopt a blanket policy to omit the prescription of antirelapse therapy altogether. Adherence to standard primaquine regimens in some studies has been reported to be acceptable (84) but outside of study settings is almost certainly poor (85). The latter represents perhaps the greatest pragmatic challenge to the successful deployment of radically curative therapy. Outside of Oceania, a short course of directly observed, high-dose primaquine (1mg/kg/day) administered over 7 days has been shown to be well-tolerated and can reduce relapses by day 28 from 50% to 4% (86, 87). If the tolerability and safety of short-course, high-dose primaquine regimens can be assured in other population groups, a new primaquine regimen could be of great benefit in improving adherence to and thus effectiveness of antirelapse therapy. Education campaigns and routine direct observation of therapy may also be beneficial and warrant further investigation.

The 8-aminoquinolines, primaquine and pamaquine, are more effective when co-administered with chloroquine or quinine than when given alone (88). The reasons for this apparent potentiation of effect are not clear. There is a hypothetical concern that schizontocidal drugs other than quinine and chloroquine may not have this potentiating effect (51). Definitive evidence for a difference in potentiation will require large, randomized studies with supervised drug administration and long-term follow-up.

Once radical cure of *P. vivax* can be reliably and safely ensured, novel deployment strategies can be considered to reduce the overall burden of vivax malaria. Individuals infected with hypnozoites and/or undetectable or asymptomatic asexual parasitemia, constitute a major reservoir of infection – most obviously manifested by high rates of *P. vivax* recurrence following treatment for supposedly pure *P. falciparum* infections (62). Two potential strategies for reducing the transmission potential of these individuals are worthy of intensive investigation. The first is to provide primaquine therapy as part of mass schizontocidal drug treatment campaigns in co-endemic regions. The second is to provide effective anti-hypnozoite treatment to *all* patients with malaria in co-endemic regions rather than just those with *P. vivax* infections (62).

Conclusions

The chemotherapy of *P. vivax* has changed little over the last 50 years and there are few novel interventions on the horizon. This situation is totally unacceptable in an era when funding for malaria research is at an all-time high. Several high priority areas of research (outlined in Box 1) must be addressed if we are to have a realistic chance of eliminating vivax malaria.

Plasmodium falciparum is resistant to chloroquine in most endemic regions and although slower to appear, chloroquine-resistant *P. vivax* strains are spreading throughout the world. In regions where *P. vivax* and *P. falciparum* cohabit, a unified treatment policy for malaria of any parasitological cause is likely to confer the greatest individual and public health benefit. Artemisinin combination therapies are highly efficacious against both species (except for parts of Cambodia) and are therefore prime candidates for unified treatment. Slowly-eliminated ACTs can suppress the first relapse of tropical strains of *P. vivax,* but whether this reduces transmission in the long term remains to be proven. The most important potential chemotherapeutic means of interrupting transmission of vivax malaria will be radical cure and thus prevention of all future relapses by using hypnozoitocidal medication.

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Primaquine is the only licensed drug for this purpose, but there are significant operational challenges in its use. The hypnozoitocidal drug discovery pipeline is virtually bare, hence optimizing the safety and effectiveness of primaquine through development of rapid diagnostic tests for G6PD deficiency and improving drug adherence are high priorities in the fight against vivax malaria.

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Abbreviations

CQR chloroquine resistance

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Box 1 Research Priority Areas for the Treatment of *P. vivax* infection

Treatment of Erythrocytic Stages

- Investigate the relative advantages and disadvantages of an extended period of post-treatment prophylaxis provided by slowly eliminated drugs.
- Investigate the impact of intermittent preventive treatment on vivax malaria in infancy, childhood and pregnancy.
- Establish the overall cost-effectiveness of a unified ACT-based treatment strategy for vivax and falciparum malaria in co-endemic regions.
- Establish the efficacy, safety and haematological effects of intravenous artesunate for the treatment of patients with severe vivax malaria.
- Investigate the efficacy of novel schizonticidal agents against both multidrug-resistant falciparum and vivax malaria.

Treatment of Exoerythrocytic Stages

- Develop robust, accurate and affordable point-of-care diagnostics for G6PD deficiency.
- Develop new compounds for the eradication of *P. vivax* hypnozoites.
- Assess the efficacy, effectiveness and safety of novel approaches to deliver primaquine treatment regimens (e.g. short-course / high-dose regimens, directly observed therapy, patient education campaigns).
- Assess the impact of routine use of effective anti-relapse therapy in high transmission settings
- Establish the safety profile of primaquine in patients with different degrees of G6PD deficiency.
- Assess the utility of primaquine radical cure for *P. vivax*, following falciparum as well as vivax malaria in co-endemic regions.
- Confirm the efficacy of primaquine when co-administered with different artemisinin combination therapies.
- Investigate the impact of primaquine prescription as part of mass drug administration for reducing *P. vivax* transmission.

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Key Points

- A unified treatment policy for malaria of any parasitological cause will confer significant individual, public health and operational benefits in regions coendemic for P. falciparum and P. vivax.
- Slowly-eliminated ACTs offer post treatment prophylaxis against the first relapse of tropical strains of P. vivax, which in the short term reduces the risk of anaemia and the transmissibility of the parasite.
- Ensuring adherence to a complete course of primaquine is the greatest challenge in the control of P. vivax malaria, and may be achieved by adopting short-course, high-dose regimens.
- A robust bedside test for G6PD deficiency is urgently needed to define the toxicity profile of primaquine and facilitate the safe deployment of antirelapse therapy.

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Table 1

Stage specificity of antimalarial agents active against *Plasmodium vivax*

Mosquito	Sporontocidal	DHFR inhibitors Atovaquone Primaquine Tafenoquine Bulaquine [1]
Human	Hypnozoitocidal	Primaquine Tafenoquine Bulaquine
	Blood schizontocidal	Artemisinins Lumefantrine Atovaquone DHFR inhibitors DHPS inhibitors [2] Quinolines [3] Antibiotics Primaquine Tafenoquine Bulaquine [1]
	Gametocytocidal	All drugs with asexual activity are gametocytocidal against *Plasmodium vivax*

Abbreviations: DHFR; dihydrofolate reductase, DHPS; dihydropteroate synthetase.

[1] Bulaquine is metabolised to primaquine; similar activity inferred.

[2] Sulfadoxine has intrinsically weak activity against *Plasmodium vivax.*

[3] Includes quinine, chloroquine, amodiaquine, mefloquine, piperaquine and pyronaridine (excludes hypnozoitocidal quinolines).