

Relapses of *Plasmodium vivax* malaria threaten disease elimination: time to deploy tafenoquine in India?

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INTRODUCTION

Millions suffer from the scourge of malaria across the world, reflected by the estimated 228 million cases and 0.4 million deaths it caused in 2018, as reported in the World Malaria Report 2019. India and African nations shouldered 85% of the world's malaria burden in 2018. The South-East Asia Region recorded a 70% decrease in malaria incidence from 2010 (17 cases/1000 population) to 2018 (5 cases/1000 population). Despite the absolute reduction in India's malaria cases, with 2.6 million fewer cases in 2018 than in 2017, India's malaria burden still remains considerable at an estimated 6.7 million cases.¹ Out of all the global *Plasmodium vivax* burden, 53% is in the WHO South-East Asia Region, India accounting for 47% and is a major cause of health burden in these countries.¹ *P. vivax* malaria is now known to cause considerable morbidity and mortality due to severe malaria.² In addition, due to relapses *P. vivax* causes additional burden on disease burden and feeds transmission. Despite the problem of *P. vivax*, malaria control have hitherto focused more on *P. falciparum*. It is likely that this burden will increase in 2020–2021 due to diversion of public health attention towards COVID-19. At the same time, there is a potential for several cross-learning between malaria and COVID-19.^{3,4} Nonetheless, *P. vivax* continues to be a pressing health-care issue and may prove to be a challenge in India, which along with Indonesia and Pakistan accounts for >80% of the global *P. vivax* burden.⁵ As per the Indian national statistics the country reported ~338K malaria cases in 2019 of which ~181K (53%) were caused by *P. vivax*. Among the top 20 districts with highest Annual Parasite Incidence (out of a total of 721 malarious districts) cases in five districts had >70% burden due to *P. vivax* in 2019.⁶ This trend can seriously undermine the efforts of Indian government towards malaria

Summary

- ▶ India reported 181,554 malaria cases caused by *Plasmodium vivax* in 2019 and WHO estimates point out that almost half of global vivax burden is in India.
- ▶ Current treatment of vivax malaria by 3 days of chloroquine and 14 days of low dose of primaquine suffers from poor compliance.
- ▶ The incomplete clearance of vivax reservoir pose a threat to India's and regional malaria elimination plans.
- ▶ Tafenoquine as an alternative to primaquine may overcome some of the challenges to malaria elimination.

elimination notwithstanding the highly impressive decline in India's disease burden.

THE TWO DOMINANT MALARIA PARASITES

P. falciparum and *P. vivax* both cause blood stage infections that can last up to years.⁷ The mechanisms of parasite growth such as asexual merozoites invading red blood cells, replicating every 48 hours and the acquisition of partial immunity result in complex infection dynamics.⁸ In addition to this, *P. vivax* has another mechanism for persisting that is, via the reservoir of hypnozoites, that lay dormant in the liver. After the introduction of *P. vivax* sporozoites into the blood, from an infected mosquito, some of the sporozoites become hypnozoites and lie dormant in the liver for as long as years until they get activated to initiate fresh blood-stage infections, and this cycle continues, much to the detriment of the patient.⁷ Reactivation of hypnozoites of *P. vivax* lead to blood-stage infections, known as relapses, are the distinctive feature between the two *Plasmodium* species.⁷

Artemisinin combination therapy (ACT) is the established therapeutic plan for *P. falciparum* (against schizonts) which targets blood-stage infection. However, ACT or chloroquine



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(CQ) alone do not suffice in treating *P. vivax* (or *P. ovale*) completely since they are not active against hypnozoites lying dormant in the liver. If left untreated, these hypnozoites increase the incidence of infection and this in turn feeds transmission. For ~75 years, since its discovery in the 1940s, primaquine (PQ) has been the only licensed drug in humans for the clearance of *P. vivax* hypnozoites. The radical treatment for *P. vivax* in India is treatment with CQ for 3 days, plus PQ for 14 days.⁶

There are several impediments to the complete and successful treatment of *P. vivax* malaria. A few notables are (1) poor compliance of the 14 day regime of PQ: since patients usually get symptomatic relief within a few days of starting CQ, they tend not to complete the PQ treatment plan of 14 days.⁹ Supervision of scheduled intake of PQ by healthcare workers is also far from adequate in India.⁹ (2) Glucose-6-phosphate dehydrogenase (G6PD) deficiency: PQ can have major adverse effects by causing dose associated acute haemolytic anaemia in individuals with G6PD deficiency.⁵ Hence, WHO recommends G6PD testing before PQ administration as the best practice and standard radical treatment of daily PQ not to be given to patients who are G6PD deficient.¹⁰ National-level estimates of G6PD deficiency in India are not available but studies suggest that the average prevalence may be ~9.8% in tribal populations and ~7.3% in other groups.¹¹ In India, there is higher prevalence of G6PD deficiency in the malarious states of Maharashtra, Odisha, Uttar Pradesh and Rajasthan.¹¹ Indian national guidelines mandate testing for G6PD deficiency wherever possible, but in the absence of any reliable point of care test and the limitations of overstretched and underdeveloped healthcare systems in India, the actual deployment rate of these tests remains largely unknown. Monitoring of haemolysis and thus the drop in haemoglobin levels needs a vigilant healthcare system, especially in the backdrop of wide prevalence of anaemia in India. (3) PQ use contraindications in pregnant and lactating mothers leave aside a large proportion of malaria patients who are thus incompletely treated and remain susceptible to *P. vivax* relapses. (4) There remains an unknown burden of relapses and asymptomatic malaria including undetected *P. vivax* cases due to low parasitaemia in India as no nationwide data are available for either. Monitoring of *P. vivax* patients, not only for ensuring compliance to 14 days of PQ treatment, but also for development of relapses thus remains a huge systemic gap. (5) Drug resistance: the mechanism of resistance for eight aminoquinoline compounds like PQ has not been fully addressed in comparison to resistance patterns in CQ that are better studied and understood.¹² Treatment failure (relapse occurrence) is usually confused as PQ resistance. There is no confirmed evidence of genuine resistance to PQ. Baird and Hoffman have published instances of PQ¹² treatment failure in patients on 5 days of 15 mg per day of PQ, instead of the standard 14 days treatment with same dosages.¹² Therefore, the above factors may continually fuel *P. vivax* transmission in India and threaten not only

the country's objective of malaria elimination by 2030 but also regional plans of the same.

To circumvent some of the roadblocks listed above, it is proposed here that Indian national malaria elimination programme consider the safety validation under real-world conditions following G6PD testing and then possible inclusion of the antihypnozoite drug tafenoquine (TQ) that has been developed for *P. vivax* radical cure. This orally active 8-aminoquinoline was discovered in 1978 at the Walter Reed Army Institute of Research (WRAIR), USA.¹³ TQ is a synthetic analogue of PQ as it differs in the presence of a methyl group and a phenoxy group at positions 4 and 5, respectively, of the drug. It was first developed with a prophylactic intention by GlaxoSmithKline and WRAIR. WRAIR worked with the Central Drug Research Institute, Lucknow, India to test and validate TQ for radical cure (1982–1987)¹⁴ and later further advanced jointly by GlaxoSmithKline and the Medicines for Malaria Venture as a radical treatment for *P. vivax* infection.¹³ Currently, TQ is approved by the FDA (US Food and Drug Administration) and is being used in the USA under the brand name of Krintafel (150 mg tablets, GlaxoSmithKline) as radical cure for *P. vivax* and as a prophylactic (100 mg tablets, Sixty Degree Pharma) under the brand name Arakoda. It has also been approved by Therapeutics Goods Administration (TGA) in Australia since 2018 and since 2019 in Brazil (first among the malaria endemic countries) and Thailand under brand name Kozenis. Recently, Peru became the second Latin country to approve of TQ in January 2021.

PHARMACODYNAMICS AND PHARMACOKINETICS OF TQ

TQ is similar to PQ in drug activity against the pre-erythrocytic forms within the liver. In addition, it is potent against both asexual and sexual parasite forms in the blood. However, TQ differs from PQ due to its longer half-life, which supports its use as a single-dose drug. TQ shows extensive protein binding of >99.5% and has a distribution volume of ≈1600 L for the prophylactic dose. PQ on the other hand shows protein binding of 75% and a volume of distribution of 150–250 L. Thus, with an oral clearance of ≈3 L/hours, TQ has an average terminal half-life of ~15 days as opposed to that of PQ which is 4–6 hours.¹⁵ PQ activity is known to vary significantly with CYP2D6 genotype activity. However, there are no conclusive studies to demonstrate the dependence of TQ activity on CYP2D6 activity though some early studies¹⁶ indicate so but it is yet to be confirmed. According to a study by Paradkar in 2018, the impaired CYP2D6 *10 allele prevalence was 19.2% in the Indian population¹⁷ which may have implications on eight aminoquinoline efficacy. While the effects of TQ on renal or hepatic impairment and their consequent effect on pharmacokinetics of TQ have not been studied, the pharmacokinetic profile of TQ remains unaffected by age, sex, ethnicity and body-weight.¹⁸ Drug interaction studies have concluded that

the pharmacokinetics of TQ were not affected on coadministration with CQ, dihydroartemisinin-piperazine or artemether-lumefantrine.¹⁸

POSSIBLE MECHANISMS OF TQ ACTION AND G6PD DEFICIENCY

Though the mechanism(s) of action responsible for TQ's antiparasitic activities remain unknown, studies on protozoan parasites, including *P. falciparum*, have suggested that TQ may interfere with mitochondrial functions and lead to apoptotic-like death of the organism. It has also been suggested that TQ may also show its effect by inhibiting hemozoin polymerisation.¹⁹ In addition to its antiparasitic activities, TQ causes red cell shrinkage and eryptosis or suicidal erythrocyte death, a process similar to apoptosis in nucleated cells.¹⁸ TQ has also shown activity against sporogonic forms of *P. vivax* at doses of more than or equal to 25 mg/kg.²⁰

As an 8-aminoquinoline, TQ like PQ causes dose-dependent, drug-induced haemolysis in individuals with G6PD deficiency, an X-linked enzyme deficiency thought to affect around 400 million people across the globe.²¹ Its slow elimination has a protracted oxidant effect and therefore TQ can be used in individuals whose G6PD enzyme activity is >70% of normal.⁵ It is apparent that TQ usage will require G6PD testing that can quantify G6PD enzymatic activity. Herein lies the challenge for malaria control programmes, but this can be overcome by introducing widespread G6PD testing, in ways applicable to the field.

A reduction in haemoglobin of >30.0 g/L, or ≥30% from baseline, or haemoglobin <60.0 g/L was the primary outcome in the Phase 3 supportive safety study of CQ+TQ versus CQ+PQ.²² The available G6PD rapid qualitative tests in the market use a limit of 30%–40% of normal G6PD activity as a cut-off to define a subject as G6PD deficient⁹ and hence will not be applicable for TQ usage which needs a minimum of 70% G6PD activity, in comparison to PQ which needs 30%.¹⁰ These values identify the G6PD deficient genotype in male hemizygotes and female homozygotes; the group at most risk of severe haemolysis with drug use. Heterozygous females who possess 30%–80% of normal G6PD enzyme activity (intermediate activity) exhibit results which are difficult to slot on qualitative tests as normal or deficient.¹⁰ The severity in reduction of haemoglobin documented after TQ exposure is dependent on the level of G6PD enzyme activity. The greatest decline has been observed in those with low G6PD activity such as hemizygous males and homozygous females besides those who are WHO class II variants.²³ In India, the latter dominate.²⁴ Finally, TQ is contraindicated for use in pregnant and lactating mothers, in breastfeeding infants and patients below the age of 16 years. TQ is contraindicated in pregnant and lactating women which could constitute a substantial proportion of population, and even if TQ is distributed with great coverage, a substantial proportion, as in the case of PQ, will be left untreated. Under the national

guidelines, PQ is contraindicated in infants and pregnant women. Follow-up of these groups is recommended under the programme and PQ administered post delivery, once the G6 PD status of the neonate is known. CYP2D6 is not assessed in the national programme. Clearly these are some gaps in the management of vivax malaria and risk of relapses. WHO recommends that G6PD deficient patients to be treated with 0.75 mg/kg body weight weekly over a period of 8 weeks. TQ should also not given in patients with a history of psychiatric disorders at doses higher than the approved dose or in patients with known hypersensitivity to 8-aminoquinolines.¹³

INTERNATIONAL TQ TRIALS

Until today, >30 clinical studies/trials have been conducted using TQ as an antimalarial agent that targets both *P. vivax* relapses and *P. falciparum*. In 1998, the first successful clinical trial was reported.¹³ There are three key studies that have established single dose of 300 mg of TQ as radical treatment of *P. vivax* malaria when in combination with the standard CQ regimen. These are:

- ▶ DETECTIVE, Part 1 (NCT01376167)²⁵: The Dose and Efficacy Trial Evaluating Chloroquine and Tafenoquine in Vivax Elimination Part 1. Single doses of 50, 100, 300 and 600 mg TQ and 3 days of CQ were compared with PQ at the dose of 15 mg/day for 14 days and 3 days of CQ and CQ alone in the third arm.
- ▶ DETECTIVE, Part 2 (NCT01376167)²⁶: The Dose and Efficacy Trial Evaluating Chloroquine and Tafenoquine In Vivax Elimination Part 2. Single dose of 300 mg TQ and 3 days of CQ was compared with PQ at the dose of 15 mg/day for 14 days and 3 days of CQ and CQ alone in the third arm.
- ▶ GATHER (NCT02216123)²²: The Global Assessment of Tafenoquine Hemolytic Risk assessed the effect of single dose of 300 mg TQ and CQ versus 14-day PQ and CQ on clinically relevant haemolysis (Hb decrease of ≥30% or >30 g/L from baseline or reduction of Hb below 60 g/L).

The details of the key studies on TQ have been summarised in table 1 and further, all studies on TQ have been collated and summarised in a review by Hounkpatin *et al.*¹³ All the trials so far have suggested TQ to be a safe drug for regular use barring the contraindications.

THE WAY FORWARD FOR TQ

In light of the distinctive edge TQ has over PQ, it is important that measures and mechanisms are devised to overcome the hurdles in deployment of TQ in India. Some notables are: (1) to resolve the issue of detection of G6PD enzyme activity via a portable point of care device that has been developed by SD BIOSENSOR. This product has been granted import permission by Ministry of Health and Family Welfare and is being marketed in India. Its clinical validation in India (Kolkata) has been completed and results are awaited. It is also under regulatory review by US FDA and AU TGA though it has been

Table 1 Key tafenoquine trials

S. no	Trial/study	Place/year	Total no. of participants	Recurrence free rate of CQ+PQ	Recurrence free rate of CQ+TQ (single dose)
1.	DETECTIVE Part 1 NCT01376167 Phase IIb/III trial ²⁵	Brazil Peru India Thailand 2011–2013	329 total	77% (95% CI 63% to 87%)	50 mg: 58% (95% CI 43% to 70%) 100 mg: 54% (95% CI 40% to 66%) 300 mg: 89% (95% CI 77% to 95%) 600 mg: 92% (95% CI 80% to 97%)
2.	DETECTIVE Part 2 NCT01376167 Phase III Trial ²⁶	Brazil Peru Colombia Thailand Philippines Ethiopia 2015–2016	522 total	70% (95% CI 60% to 77%)	62% (95% CI 55% to 69%)
3.	GATHER NCT02216123 Phase III Trial ²²	Brazil Colombia Ethiopia Peru Thailand Vietnam 2014–2016	251 total	75% (95% CI 64% to 83%)	73% (95% CI 65% to 79%)

CQ, chloroquine; PQ, primaquine; TQ, tafenoquine.

already approved by the Global Fund Expert Review Panel.²⁷ Approval for TQ use under Indian national programme is under review (2) to impart additional training to healthcare workers to use the point-of-care test before TQ usage and PQ use as per national guidelines. Compliance can be ensured by Directly Observed Therapy as is being done in other disease elimination programmes like Tuberculosis and Lymphatic Filariasis. (3) to make provisions for additional costs of TQ due to mandatory G6PD testing to Indian healthcare system though these will decrease as the drug begins to be used widely. The G6PD test and TQ tablet together will cost ~ US\$ 1.40 which is at par with the cost of PQ that sells at ~ US\$ 1. The price in India and other endemic countries is volume-based assuming an annual production of 1 million doses. The Indian costs is a not-for-profit price based on manufacturing costs alone (personal communication). Undoubtedly, the costing is of lower significance in context of the aimed elimination of malaria from India. It is vital to reduce *P. vivax* transmission by clearing reservoirs of parasites that cycle via relapses and thus to protect those for whom radical cure with either PQ or TQ is contraindicated.

In conclusion, *P. vivax* infection remains endemic in India despite huge gains in its control over the past two decades. Data suggest that the elimination of *P. vivax* foci can be achieved but not in less than 3 years, compared with the 1 year for *P. falciparum*.²⁸ Hence, India needs to deploy all new malaria control tools like G6PD testing and TQ to continue to stem this scourge. The current treatment protocol of CQ plus PQ for 14 days has substantial concerns attached to its poor compliance and possible drug resistance. Due to this, TQ provides a

good alternative and maybe considered further in India. The adoption of TQ in the current Indian healthcare scenario may address the excessive burden India bears of world's *P. vivax*.

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