Introduction

*Plasmodium vivax* is the most common species of *Plasmodium* responsible for majority of cases of malaria worldwide. *P. vivax* malaria is a major problem in various countries such as Southeast Asia and Horn of Africa. Globally, an estimated 219 million cases of malaria were reported in 2017 and 3.4 per cent of estimated malarial cases were caused by *P. vivax* malaria. Approximately 82 per cent of the world wide *P. vivax* cases were reported from India, Pakistan, Ethiopia, Indonesia and Afghanistan in the year 2017. The estimated mortality rate associated with *P. vivax* malaria ranged between 4 and 39 per cent of all malaria related deaths outside sub-Saharan Africa. *P. vivax* malaria has the ability to remain in the liver as a dormant form (hypnozoite) which is responsible for relapse of *P. vivax* malaria; hence it is necessary to target both the blood (schizont) as well as the liver (hypnozoite) stages of *P. vivax* to prevent its relapse. A number of factors limit the use of primaquine (PQ), the currently available therapy for *P. vivax* (hypnozoite stage), such as haemolysis in glucose-6-phosphate dehydrogenase-deficient patients and being contraindicated in pregnant women. Another problem associated with PQ is the poor adherence rate to the 14-day treatment regimen. Single-dose tafenoquine (TQ), an 8-aminoquinoline, has recently been approved by the U.S. FDA for the treatment of *P. vivax* malaria along with a blood schizonticidal. TQ is active against all stages of *P. vivax* lifecycle. In published studies, TQ is considered a better alternative to PQ in terms of adherence, but there are some concerns regarding its safety, efficacy and study designs of trials conducted on TQ. In this context, this review, discusses the potential safety concerns, efficacy data, summary and an appraisal of findings of the important published trials of TQ.

Key words 8-aminoquinoline - efficacy - malaria - *Plasmodium* - primaquine - safety - tafenoquine
Efficacy of tafenoquine observed in various studies

In a randomized, open-label, prospective dose-ranging study of safety and efficacy of TQ in prevention of \textit{P. vivax} malaria conducted by Walsh \textit{et al} \textsuperscript{17}, 44 patients were randomly divided into four groups, \textit{i.e.} TQ 300 mg daily for seven days, TQ 500 mg daily for three days repeated one week after initial dose, TQ 500 mg single dose and CQ alone group. Patients were followed up for six months. The primary efficacy end point was occurrence of microscopically proven \textit{P. vivax} malaria after treatment. Only one relapse each occurred in the TQ 500 mg daily for three days and TQ 500 mg single-dose groups, however, four relapses were seen in the CQ alone group.

In another randomized, open-label, prospective study conducted by Walsh \textit{et al} \textsuperscript{14}, safety and efficacy of TQ were assessed in \textit{P. vivax} malaria patients. Eighty subjects with \textit{P. vivax} malaria were randomly divided into five groups and followed up for 24 wk. The patients were given TQ 300 mg per day for seven days (n=18), TQ 600 mg per day for three days (n=19), TQ 600 mg single dose (n=18), no treatment (n=13) and PQ 15 mg per day for 14 days (n=12). All participants received 1500 mg of CQ over three days. There were eight relapses in the CQ alone group, three relapses in the CQ plus PQ group, while only one relapse was seen in the CQ plus TQ group. They also found that protective efficacy with CQ plus TQ regimen was 98.5 per cent as compared to 79.5 per cent with CQ plus PQ.

Walsh \textit{et al} \textsuperscript{14} in another randomized, open-label, prospective study randomized 104 patients to receive a loading dose of TQ 400 mg daily for three days, followed by TQ 400 mg once a month for five months, and 101 patients to receive a placebo. The protective efficacy of TQ against all malaria infections was 97 per cent and for \textit{P. vivax} malaria was 96 per cent.

Elmes \textit{et al} \textsuperscript{15} assessed the efficacy of three different doses of TQ for three days in \textit{P. vivax} malaria as a post-exposure prophylaxis versus PQ plus doxycycline in Bougainville and Timor Leste. The relapse rate in subjects treated with TQ in Bougainville was 1.2 (200 mg twice daily for three days) and 2.3 per cent (400 mg once daily for three days), respectively and in case of PQ plus doxycycline it was 3.4 per cent. The observed relapse-free efficacy in subjects treated with TQ in Timor Leste subjects was 4.9 (200 mg once daily for three days), 5.3 (200 mg twice daily for three days) and 11 per cent (400 mg once daily for three days) respectively and in case of PQ plus doxycycline it was 10 per cent.

In a phase 2b, double-blind, double-dummy, randomized placebo-controlled trial conducted on microscopically confirmed \textit{P. vivax} malaria patients in four countries (India, Brazil, Peru and Thailand), Llanos-Cuentas \textit{et al} \textsuperscript{16} evaluated the single-dose efficacy of different doses of TQ (50 mg, 100 mg, 300 mg and 600 mg) with CQ combination. The relapse-free efficacy with different doses of TQ at six months was 57.7 (50 mg), 54.1 (100 mg), 89.2 (300 mg) and 91.9 per cent (600 mg), respectively which was better compared with CQ plus PQ at 77.3 per cent.

In another randomized controlled trial study conducted by Llanos-Cuentas\textsuperscript{17}, analysis of phase 3 data regarding efficacy and safety outcomes was done along with patient-level meta-analysis for the number of patients who were free from recurrence at six months. In the efficacy part, it was reported that 67 and 72.8 per cent of patients were free from recurrence at six months in the TQ and PQ groups, respectively. They concluded that TQ failed to show non-inferiority as compared to PQ.

Similar results were also observed in another study by Fukuda \textit{et al} in Bangkok and Thailand. Relapse-free efficacy at 120 days with 400 mg TQ for three days
alone was 100 per cent compared to the CQ (2500 mg) plus PQ group at 95 per cent.

A phase 3 double-blind, double-dummy, randomized placebo-controlled trial was conducted in Ethiopia, Peru, Brazil, Cambodia, Thailand and Philippines by Lacerda et al in microscopically confirmed P. vivax malaria. This trial concluded that single-dose TQ was slightly less efficacious than PQ in intention-to-treat and per-protocol population. The observed relapse-free efficacy of TQ at six months in intention-to-treat population was 62.4 per cent and that of CQ plus PQ was 69.6 per cent. Relapse-free efficacy at six months in per-protocol population was 62.2 and 70.5 per cent in the TQ and PQ plus CQ groups respectively.

In a randomized double-blind active-controlled phase 3 trial conducted by Nasveld et al to evaluate the safety, tolerability and efficacy of TQ vs. mefloquine for malaria prophylaxis in non-immune subjects, Australian soldiers were administered weekly TQ in a dose of 200 mg or mefloquine in a dose of 250 mg for six months during their stay in East Timor, and after returning to Australia, the TQ group was given a placebo and the mefloquine group received 30 mg PQ for 14 days. In this study, after 20 weeks discontinuation of the treatment, four relapse cases of P. vivax occurred in the TQ group as compared to one case in the mefloquine group.

**Potential safety concerns of tafenoquine**

TQ is a synthetic analogue of PQ, both belongs to the category of 8-aminoquinolines and have potential to cause haemolysis in G6PD-deficient patients. The use of TQ is linked with a risk of developing haemolytic anaemia and methaemoglobinemia. Side effects associated with the use of TQ (found in clinical trials) include gastrointestinal disorders (upper abdominal pain and diarrhoea), decrease in haemoglobin level and neurological problems (headache and dizziness). Apart from this, it has been shown that a higher dose of TQ is associated with development of eye-related disorders such as keratopathy and retinal disorders. Other side effects of TQ were comparable to PQ. These adverse effects may lead to impaired quality of life and poor treatment compliance to TQ. However, no clinically significant safety or interactions were seen with co-administration of CQ and TQ in healthy subjects. The important safety concerns associated with TQ and their frequency reported in different clinical trials are given in Table.

**Summary & appraisal of findings of the important published trials of tafenoquine**

Many research reports have been published regarding the role of TQ in the management of P. vivax malaria. Although many reports suggest a promising effect of TQ with reasonable safety, still there remain certain areas of concern regarding the conduct of the studies as well as some safety issues, which makes TQ a less preferred option.

For example, as discussed earlier, although Walsh et al showed that relapse-free efficacy was shown to be higher in the TQ groups as compared to the CQ alone group and TQ was shown to be safe in preventing relapse of P. vivax malaria, the major limitation of this study was the small sample size, and patients were subjected to the CQ alone group were not prescribed PQ which is the standard of care in preventing relapse of P. vivax. Although TQ has been shown to be a safe drug, during this study, 22 episodes of bloody diarrhoea were reported which resolved after administration of oral rehydration solution. Similarly, limitation and PQ exclusion was also noted in another study by Walsh et al. Here, higher number of subjects experienced neurological and gastrointestinal adverse effects in the TQ group. Furthermore, in yet another study, although Walsh et al demonstrated the protective efficacy of TQ against all malaria infections, TQ led to a greater number of adverse events such as nausea and diarrhoea (calculated as adverse events ≥1), as compared to the placebo group.

Elmes et al conducted a study for a period of two months to study the efficacy and safety of three different regimens of TQ and PQ plus doxycycline for post-exposure prophylaxis of P. vivax. The authors concluded that TQ is a safe and well-tolerated medication for P vivax malaria. The relapse rate was lowest with TQ 200 mg twice daily as discussed earlier, however, the limitation of this study was again the relatively small number of subjects who had relapse of P. vivax, hence one needs to be cautious while interpreting the efficacy comparisons.

In the study by Nasveld et al as discussed earlier, both treatment regimens were well tolerated, but TQ was significantly associated with keratopathy as compared to mefloquine (69 vs. 0). This mild keratopathy disappeared after one year without affecting the visual acuity. There were no symptomatic malarial infections seen in either group during the prophylactic phase, however, 0.9 per cent of subjects in the TQ group as
| Trials                  | Hb decreased (%) | Methaemoglobinemia (%) | Dizziness (%) | Headache (%) | Abdominal pain (%) | Diarrhoea (%) | Remarks                                      |
|------------------------|------------------|------------------------|---------------|-------------|-------------------|--------------|----------------------------------------------|
| Walsh et al<sup>13</sup>, 2004 | -                | -                      | 22            | 17          | 6                 | -            | CQ + TQ 300 mg arm (n=18) o.d. × seven days  |
|                        |                  |                        | (TQ 300 mg)   |             |                   |              | CQ + TQ 600 mg arm (n=19) o.d. × three days  |
|                        |                  |                        | 21            | 5           | 16                |              | CQ + TQ 600 mg arm (n=18) o.d. single dose   |
|                        |                  |                        | 11            | 0           | 8                 |              | CQ + PQ 15 mg arm (n=12) o.d. × 14 days      |
|                        |                  | 33 (PQ 15 mg o.d. × 14 days) |              |              |                   |              |                                               |
| Walsh et al<sup>14</sup>, 2004 | -                | -                      | 21.2 (TQ)     | 10.6 (TQ)   | 30.8 (TQ)         | 7.9 (placebo)| TQ, loading dose 400 mg daily × three days,  |
|                        |                  |                        | 24.8 (placebo)| 8.9 (placebo)|                   |              | followed by 400 mg once a month for five     |
|                        |                  |                        |               |              |                   |              | months (n=104)                               |
|                        |                  |                        |               |              |                   |              | Placebo (n=101)                              |
| Elmes et al<sup>15</sup>, 2008 | -                | -                      | 7.4 (TQ 400 mg, o.d.) | 17.4 (TQ 400 mg, o.d.) | 9.5 (TQ 400 mg, o.d.) | -            | (n=104)                                      |
|                        |                  |                        | 3.1 (TQ 200 mg, b.i.d.) | 10.6 (TQ 200 mg, b.i.d.) | 14.9 (TQ 200 mg, b.i.d.) | -            | Placebo (n=101)                              |
|                        |                  |                        | 1.0 (TQ 200 mg, o.d.) | 6.4 (TQ 200 mg, o.d.) | 4.7 (TQ 200 mg, o.d.) | -            |                                               |
|                        |                  |                        | 1.9 (DC)      | 3.2 (DC)    | 2.2 (DC)          |              |                                               |
| Nasveld et al<sup>16</sup>, 2009 | 1 (TQ)           | 12 (TQ)                | 5 (TQ)        | 16 (TQ)      |                   |              | TQ (n=492), 200 mg dose × six months MQ arm (n=162), 250 mg × six months |
|                        |                  | 1 (MQ)                 | 12 (MQ)       | 8 (MQ)       | 19 (MQ)           |              |                                               |

Contd…
### Trials

| Trials | Hb decreased (%) | Methaemoglobinemia (%) | Dizziness (%) | Headache (%) | Abdominal pain (%) | Diarrhoea (%) | Remarks |
|--------|------------------|-------------------------|---------------|--------------|-------------------|---------------|---------|
| Miller *et al* 2013 | -                | -                       | 15 (CQ)       | 35 (CQ)      | 5 (CQ)            | 15 (CQ)      | CQ alone group (n=20) 600 mg given day 1-2 and 300 mg on day 3 TQ alone group (n=20) 450 mg given days 2 and 3 CQ + TQ group (n=18) consisting of the following regimen CQ 600 mg given on day 1 CQ 600 mg + TQ 450 mg on day 2 CQ 300 mg + TQ 450 mg on day 3 |
| Llanos-Cuentas *et al* 2014 | 0 (TQ 50 mg) | 0 (TQ 50 mg) | 13 (TQ 50 mg) | 25 (TQ 50 mg) | 11 (TQ 50 mg) | 7 (TQ 50 mg) | TQ + CQ (n=57), single 300 mg dose of TQ given on day 1 or 2 CQ + PQ (n=50) PQ 15 mg o.d. × 14 days CQ 600 mg given on day 2 and 300 mg on day 3 in both groups |
| Fukuda *et al* 2017 | 4.3 (TQ) | 47.8 (TQ) | 26.1 (TQ) | 30.4 (TQ) | 13 (TQ) | 6.5 (TQ) | TQ 400 mg (n=46) o.d. × three days CQ + PQ (n=24) CQ 1000 mg given on day 1-2 and 500 mg given on day 3, PQ 15 mg o.d. × 14 days |

*Contd...*
compared to 0.7 per cent in the mefloquine group, had relapse of malarial infection during follow-up. The authors concluded that TQ 200 mg weekly dose is safe and well tolerated in non-immune subjects following six months of prophylaxis and TQ can be used as a weekly antimalarial without the need of other drugs after leaving an endemic area. The major limitation of the study was however, that the precise exposure to malaria could not be proved.

In the phase 2b study by Llanos-cuentas et al\textsuperscript{16}, as discussed earlier, the relapse-free efficacy was higher at doses of 300 and 600 mg of TQ as compared to 50 and 100 mg (maximum at dose of 600 mg) respectively. However, enrolling CQ alone group (n=54) and depriving these subjects from the standard of care for radical cure of \textit{P. vivax} malaria, does not seem to be meaningful. Incidence of diarrhoea was highest with the TQ 600 mg group (16% patients compared to 8% in the PQ group). Four patients in the PQ group and two each in the TQ 50 mg, 100 mg and CQ alone groups and one in the TQ 300 mg group, had QT prolongation. In subjects receiving TQ, four had haemoglobin decline of more than 25 per cent from baseline, one patient each on PQ and CQ had the similar decline in haemoglobin. No events of methaemoglobinaemia were reported in the TQ group (seen in one subject in the PQ group). The authors concluded that TQ as a single-dose treatment along with CQ is capable of preventing \textit{P. vivax} relapse effectively and it seems to be a potential drug candidate for the first-choice treatment of uncomplicated \textit{P. vivax} malaria.

In the phase 2b trial conducted by Fukuda et al\textsuperscript{9}, the efficacy and safety of the three-day course of TQ monotherapy (n=46) was evaluated and compared with PQ plus CQ (n=24). However, CQ was not given along with TQ. The primary end point was day 28 clinical response and the secondary end point was proportion of patients without \textit{P. vivax} re-emergence at 60, 90 and 120 days. There was no significant difference amongst the two treatment groups in the primary efficacy outcome at 28 days and also with respect to secondary efficacy outcome at 120 days. However, TQ as compared to PQ took a significantly longer time (mean hours) for parasite clearance (82.5 vs 40 h), with a gametocyte and fever clearance of 49.1 vs 22.7 h time and 41.1 vs 24.7 h, respectively. This observation points towards the likely resistance to TQ monotherapy. TQ showed thrombocytopenia in 13 per cent of patients as compared to none in the PQ group,
and methaemoglobinemia was observed in 47.8 per cent of patients in the TQ group as compared to none in the PQ group. TQ showed keratopathy in 31.8 per cent of patients as compared to nil in the PQ group. Although the sample size of this trial was less but it raises the question of safety and the potential risk of developing resistance to TQ. The authors concluded that TQ should not be used as monotherapy for radical cure of *P. vivax* malaria.

In the multicentre, randomized, double-blind, placebo-controlled trial by Lacerda et al., there were three treatment groups, *i.e.* TQ (along with CQ), placebo and PQ (along with CQ) groups. In the efficacy part, the authors concluded that both TQ and PQ were superior to placebo in preventing the relapse of *P. vivax* malaria. However, no direct comparison was carried out between TQ and PQ (recommended therapy for preventing relapse). In the placebo group, 133 patients in the placebo group were given only CQ. The authors compared TQ plus CQ with CQ alone and PQ plus CQ with CQ alone, however, a direct comparison between PQ plus CQ and TQ plus CQ groups could have been better to reach a more meaningful conclusion. In the safety part of this trial, it was reported that dizziness and haematological toxicity were seen in a greater number of patients in the TQ group as compared to the PQ and placebo groups. Seven patients in the TQ group met the stopping criteria for haematological toxicity. Furthermore, haemoglobin decline of more than 3 g/dl was observed in 5.4 per cent of patients in the TQ group as compared to 1.5 per cent in the placebo group and 1.6 per cent in the PQ group. Most of the adverse events were of mild-to-moderate severity in the TQ group. However, no statistical analysis was carried out for safety parameters.

In another study done by Llanos-Cuentas et al., phase 3 data on efficacy and safety outcomes was analysed, details of which were discussed earlier. In this study, in the safety part, it was found that a greater number of subjects had a decrease in haemoglobin level in the TQ group (2.4%) as compared to PQ (1.2%).

From the above discussion, it can be corroborated that there were some limitations of the research studies and safety issues of TQ which are alarming and seem to occur at a higher frequency than the main comparator PQ (standard of care for hypnozoite stage of *P. vivax*). Clinical trials or research studies involving TQ may claim similar efficacy (to PQ) and reasonable safety, but one should interpret their results with caution. Apparently single-dose regimen of TQ offers better adherence rates as compared to the 14-day treatment with PQ, however, some serious safety concerns must be weighed against the anticipatory benefits. Currently, from results of most of the clinical studies, it seems that TQ is not superior (not non-inferior) or even therapeutically equivalent to PQ, but potential safety concerns make TQ less favourable than PQ.

**Tafenoquine: implications for India**

India accounts for a large estimated *P. vivax* malaria burden. Nearly 18 per cent of the total confirmed *P. vivax* cases globally, were reported in India in 2014. This constitutes to approximately one-third of all malaria cases in India (around 380,000 confirmed cases in the public sector in 2014)\(^8\). In the recent past, *P. vivax* accounted for around half of all malaria cases. Notably, *P. vivax* is an important pathogen in children\(^20,21\). In a developing country like India, TQ can be instrumental in endemic areas in providing the radical cure against *P. vivax* malaria because single dose can be substituted for 14-day PQ treatment and this can increase the adherence rates dramatically. Moreover, introduction of TQ in the National Malaria Control Programme under the National Vector Borne Disease Control Programme (NVBDPCP) can open new ways to address the *P. vivax* malaria load in a country like India. Adherence to the two-week PQ therapy often remains poor because most of the patients stop taking PQ when the symptoms disappear. Moreover, India has large and poorly regulated private healthcare providers, who usually go for treatment of acute symptoms and do not prescribe PQ to kill the dormant malarial parasite\(^22\).

Currently, TQ is under the last stages of approval consideration by the regulatory authority of India, a randomized controlled trial registered with CTRI (Clinical Trials Registry-India, CTRI/2012/03/002511), conducted at seven sites in India, is aimed to evaluate the efficacy, safety and tolerability of TQ in subjects with *P. vivax* malaria. This is evaluating the efficacy of TQ in doses of 50, 100, 300 and 600 mg, compared with active control and placebo. The recruitment has been stopped and results are awaited\(^23\).

NCT01376167 (multicentric, double-blind, randomized, parallel-group, active-controlled study) to study the safety, efficacy and tolerability of TQ in patients with *P. vivax* malaria was registered with ClinicalTrials.gov. This was a phase 2b/3 study
involving four study sites in India and has been completed and shows promising results. Drug regimens studied in this trial include: CQ 600 mg, CQ 300 mg, TQ 50 mg, TQ 100 mg, TQ 300 mg, TQ 600 mg and PQ 15 mg.

In a meeting, held in April 2019 at the Central Drugs Standard Control Organisation (CDSCO) headquarters, New Delhi, regarding the recommendations of the subject experts committee (antimicrobial and antiviral), the TQ 150 mg tablet (GlaxoSmithKline Pharmaceuticals Ltd, Mumbai, India) proposal was discussed. The committee deliberated that even TQ has an advantage of single-dose administration for radical cure of *P. vivax* as compared to 14-day treatment with PQ, but both TQ and PQ cause haemolytic anaemia in G6PD-deficient patients and G6PD test is also recommended in case of treatment with TQ. TQ carries a significant risk of inadvertent use in G6PD-deficient subjects, and the effect of the single-dose drug will persist for a prolonged period. The committee considered instructed the firm to submit the detailed strategies or modalities to address the potential concerns so that further review of the proposal may be considered. Committee also opined that CDSCO should take opinion of NVBDCP on this issue.

In a Cochrane systematic review, it was found that TQ was able to prevent *P. vivax* malaria relapses in clinically and parasitological confirmed cases. However, TQ has not been tested in pregnant women, children and in G6PD-deficient subjects. The findings suggested that short-term use of TQ can offer a practical advantage among people without G6PD deficiency, but due to its longer half-life, it poses a risk to subjects with G6PD deficiency, when given inadvertently.

In conclusion from the above discussion, there are certain safety issues of TQ which are of concern and seem to occur at a higher frequency than PQ. Clinical trials or research studies involving TQ also appear to have certain limitations; hence their results should be interpreted with caution. Single-dose administration of TQ offers better adherence rates as compared to 14-day treatment with PQ, however, some serious safety concerns must be considered. Future research and implementation of certain mitigation strategies may address the concerns related to the safety and efficacy of TQ for the prevention of relapse of *P. vivax* malaria.

**Financial support & sponsorship:** None.

**Conflicts of Interest:** None.

---

**References**

1. Phillips MA, Burrows JN, Manyando C, van Huijsduijnen RH, Van Voorhis WC, Wells TNC. Malaria. *Nat Rev Dis Primers* 2017; 3: 17050.
2. Ebstein YA, Abay SM, Tadesse WT, Ejigu DA. Tafenoquine and its potential in the treatment and relapse prevention of *Plasmodium vivax* malaria: The evidence to date. *Drug Des Devel Ther* 2016; 10: 2387-99.
3. World Health Organization. *World Malaria Report* 2018. Geneva: WHO; 2018.
4. World Health Organization. *World Malaria Report*. Geneva: WHO; 2016.
5. Surjadiya C, Surya A, Baird JK. Epidemiology of *Plasmodium vivax* in Indonesia. *Am J Trop Med Hyg* 2016; 95: 121-32.
6. Fernando D, Rodrigo C, Rajapakse S. Primaquine in vivax malaria: An update and review on management issues. *Malar J* 2011; 10: 351.
7. World Health Organization. *Guidelines for the treatment of malaria*, 3rd ed. Geneva: WHO; 2015.
8. Lacerda MVG, Llanos-Cuentas A, Krudsood S, Lon C, Saunders DL, Mohammed R, et al. Single-dose tafenoquine to prevent relapse of *Plasmodium vivax* malaria. *N Engl J Med* 2019; 380: 215-28.
9. Fukuda MM, Krudsood S, Mohamed K, Green JA, Warrasak S, Noedl H, et al. A randomized, double-blind, active-control trial to evaluate the efficacy and safety of a three day course of tafenoquine monotherapy for the treatment of *Plasmodium vivax* malaria. *PLoS One* 2017; 12: e0187376.
10. Watson J, Taylor WRJ, Bancone G, Chu CS, Jittamala P, White NJ. Implications of current therapeutic restrictions for primaquine and tafenoquine in the radical cure of vivax malaria. *PLoS Negl Trop Dis* 2018; 12: e0006440.
11. Hounkpatin AB, Kreidenweiss A, Held J. Clinical utility of tafenoquine in the prevention of relapse of *Plasmodium vivax* malaria: A review on the mode of action and emerging trial data. *Infect Drug Resist* 2019; 12: 553-70.
12. Walsh DS, Looareesuwan S, Wilairatana P, Heppner DG Jr., Tang DB, Brewer TG, et al. Randomized dose-ranging study of the safety and efficacy of WR 238605 (Tafenoquine) in the prevention of relapse of *Plasmodium vivax* malaria in Thailand. *J Infect Dis* 1999; 180: 1282-7.
13. Walsh DS, Wilairatana P, Tang DB, Heppner DG Jr., Brewer TG, Krudsood S, et al. Randomized trial of 3-dose regimens of tafenoquine (WR238605) versus low-dose primaquine for preventing *Plasmodium vivax* malaria relapse. *Clin Infect Dis* 2004; 39: 1095-103.
14. Walsh DS, Eamsila C, Sasiprapha T, Sangkharomya S, Khiewsathien P, Supakalin P, et al. Efficacy of monthly tafenoquine for prophylaxis of *Plasmodium vivax* and multidrug-resistant *P. falciparum* malaria. *J Infect Dis* 2004; 190: 1456-63.
15. Elmes NJ, Nasveld PE, Kitchener SJ, Kociosko DA, Edstein MD. The efficacy and tolerability of three different
regimens of tafenoquine versus primaquine for post-exposure prophylaxis of *Plasmodium vivax* malaria in the Southwest Pacific. *Trans R Soc Trop Med Hyg* 2008; 102: 1095-101.

16. Llanos-Cuentas A, Lacerda MV, Rueangweerayut R, Krudsood S, Gupta SK, Kocher SK, *et al.* Tafenoquine plus chloroquine for the treatment and relapse prevention of *Plasmodium vivax* malaria (DETECTIVE): A multicentre, double-blind, randomised, phase 2b dose-selection study. *Lancet* 2014; 383: 1049-58.

17. Llanos-Cuentas A, Lacerda MVG, Hien TT, Vélez ID, Namaik-Larp C, Chu CS, *et al.* Tafenoquine versus primaquine to prevent relapse of *Plasmodium vivax* malaria. *N Engl J Med* 2019; 380: 229-41.

18. Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, *et al.* Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. *Antimicrob Agents Chemother* 2010; 54: 792-8.

19. Miller AK, Harrell E, Ye L, Baptiste-Brown S, Kleim JP, Ohrt C, *et al.* Pharmacokinetic interactions and safety evaluations of coadministered tafenoquine and chloroquine in healthy subjects. *Br J Clin Pharmacol* 2013; 76: 858-67.

20. Directorate of National Vector Borne Disease Control Programme. Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India. *Strategic plan for malaria control in India 2012–2017: A five-year strategic plan.* Available from: http://nvbdcp.gov.in/Doc/Strategic-Action-Plan-Malaria-2012-17-Co.pdf, accessed on June 30, 2019.

21. Anvikar AR, Shah N, Dhariwal AC, Sonal GS, Pradhan MM, Ghosh SK, *et al.* Epidemiology of *Plasmodium vivax* malaria in India. *Am J Trop Med Hyg* 2016; 95: 108-20.

22. The Hindustan Times. *New drug to boost India’s efforts to end malaria by 2030.* Available from: https://www.hindustantimes.com/health/new-drug-to-boost-india-s-efforts-to-end-malaria-by-2030/story-PQQXCQ4D58c7zcYn601bVO.html, accessed on June 30, 2019.

23. CTRI/2012/03/002511. Study to evaluate the efficacy, safety and tolerability of tafenoquine in subject with *Plasmodium vivax* malaria. Available from: http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=42955&EncHid=&username=TAF112582, accessed on July 4, 2019.

24. NCT01376167. Ph 2B/3 Tafenoquine (TFQ) study in prevention of vivax relapse. Available from: https://clinicaltrials.gov/ct2/show/NCT01376167, accessed on July 4, 2019.

25. Recommendations of the SEC (Antimicrobial & Antiviral) made in its 56th meeting held on 25.04.2019 at CDSCO, HQ, New Delhi. Available from: https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadCommitteeFiles/56Antimicrobial.pdf, accessed on July 4, 2019.

26. Rajapakse S, Rodrigo C, Fernando SD. Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria. *Cochrane Database Syst Rev* 2015; 2013: CD010458.

*For correspondence:* Dr Harmanjit Singh, Department of Pharmacology, Government Medical College & Hospital, Chandigarh 160 047, India  
e-mail: harman_gmcp@yahoo.com