Randomized Trial of 3-Dose Regimens of Tafenoquine (WR238605) versus Low-Dose Primaquine for Preventing Plasmodium vivax Malaria Relapse

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Background. Tafenoquine is an 8-aminoquinoline developed as a more effective replacement for primaquine. In a previous dose-ranging study in Thailand, 3 tafenoquine regimens with total doses ranging from 500 mg to 3000 mg prevented relapse of Plasmodium vivax malaria in most patients when administered 2 days after receipt of a blood schizonticidal dose of chloroquine.

Methods. To improve convenience and to begin comparison of tafenoquine with primaquine, 80 patients with P. vivax infection were randomized to receive 1 of the following 5 treatments 1 day after receiving a blood schizonticidal dose of chloroquine: (A) tafenoquine, 300 mg per day for 7 days (n = 19); (B) tafenoquine, 600 mg per day for 3 days (n = 13); (C) tafenoquine, 600 mg as a single dose (n = 18); (D) no further treatment (n = 13); or (E) primaquine base, 15 mg per day for 14 days (n = 12). The minimum duration of protocol follow-up was 8 weeks, with additional follow-up to 24 weeks.

Results. Forty-six of 55 tafenoquine recipients, 10 of 13 recipients of chloroquine only, and 12 of 12 recipients of chloroquine plus primaquine completed at least 8 weeks of follow-up (or had relapse). There was 1 relapse among recipients of chloroquine plus tafenoquine, 8 among recipients of chloroquine only, and 3 among recipients of chloroquine plus primaquine. The rate of protective efficacy (determined on the basis of reduction in incidence density) for all recipients of chloroquine plus tafenoquine, compared with recipients of chloroquine plus primaquine, was 92.6% (95% confidence interval, 7.3%–99.9%; P = .042, by Fisher’s exact test).

Conclusions. Tafenoquine doses as low as a single 600-mg dose may be useful for prevention of relapse of P. vivax malaria in Thailand.

Primaquine, an 8-aminoquinoline, is the only drug available for the eradication (“radical cure”) of the dormant hepatic stages of Plasmodium vivax malaria. However, primaquine has a narrow therapeutic range and a short half-life that necessitates daily administration for 2 or more weeks, reducing compliance with therapy [1, 2]. Moreover, there are an increasing number of reports of primaquine failure in some areas where P. vivax is endemic [1, 3–5].

Tafenoquine, formerly called “WR238605,” is a synthetic primaquine analogue that was developed by the US Army as a safer, more effective, and longer-acting primaquine alternative [6–9]. Preclinical studies involving P. vivax or P. vivax–like malaria animal models indicate that tafenoquine is significantly more active than primaquine against hepatic and erythrocytic stages and support its clinical utility [10–13]. In earlier phase 1 and 2 clinical studies, the drug was found to be safe,
well tolerated, and effective in preventing \textit{P. vivax} malaria relapse [6, 8, 9]. Previously, in the only tafenoquine dose-ranging \textit{P. vivax} radical cure study, 35 \textit{P. vivax}-infected patients were randomized to receive 1 of 3 dose regimens of tafenoquine (total dose range, 500–3000 mg) 2 days after receiving a blood schizonticidal dose of chloroquine and had low rates of relapse (the rates were significantly better than those for chloroquine alone) [6]. Of note, among 23 patients who continued follow-up for 2–6 months or until relapse, relapses were detected in 1 of 9 recipients of a split tafenoquine dose (1500 mg per week for 2 weeks)—an infection that may have been 8-aminoquinoline tolerant—and in only 1 of 7 recipients of a single 500-mg dose of tafenoquine [6]. Here, with a focus on optimizing dose regimens and increasing convenience, and to begin to define the effectiveness of tafenoquine relative to a conventional primaquine regimen, 80 patients were randomized to 1 of 5 treatment groups: 3 groups received chloroquine, followed the next day by tafenoquine (total doses of 600 mg, 1800 mg, or 2100 mg over 1, 3, or 7 days, respectively), 1 group received chloroquine only, and 1 group received chloroquine plus primaquine (15 mg base per day for 14 days).

**PATENTS AND METHODS**

**Study Design**

This was a randomized, open-label, prospective study of tafenoquine to assess its safety, tolerability, and ability to prevent relapse of \textit{P. vivax} malaria. The study was approved by the US Army Human Use Research Review Board and the Institutional Review Board of Mahidol University (Bangkok, Thailand). The protocol was part of an investigational new drug application filed with the US Food and Drug Administration and was conducted according to Good Clinical Practices guidelines. Informed consent was obtained from all patients. Study monitoring was conducted by the Quality Assurance Office, Armed Forces Research Institute of Medical Science, the US Army Medical and Materiel Development Activity (Fort Detrick [Frederick, MD]), and SmithKline Beecham Pharmaceutical Company.

**Study Site and Participants**

The study was conducted from August 1998 until June 1999 at the Bangkok Hospital for Tropical Diseases, a malaria referral center for central and northern Thailand. Male and female Thai or ethnic Burmese patients aged 18–55 years who had documented \textit{P. vivax} infection and who signed a consent form were eligible for enrollment. \textit{P. vivax} infection was defined as the presence of \textit{P. vivax} asexual stage parasites on a thin blood smear. Other enrollment criteria were a weight within 20% of the standards for the population, normal findings of a glucose-6-phosphate dehydrogenase (G-6PD) screening (methemoglobin reduction assay), the ability to take oral medication, no receipt of an antimalarial drug in the past 14 days, and a negative serum pregnancy test result. Exclusion criteria included mixed infection (\textit{P. vivax} and \textit{Plasmodium falciparum}), a hematocrit of <25%, protracted vomiting, oliguria, systolic blood pressure of <90 mm Hg, lactation, or concomitant systemic disease. Patients were asked to remain hospitalized for the duration of their treatment and then to remain in the Bangkok area, where there is no malaria transmission, for intermittent follow-up up to 24 weeks after commencing treatment.

**Interventions**

All patients received 1500 mg of chloroquine administered over 3 days (days –3 to –1) to achieve clearance of blood-stage parasites and were then randomized to 1 of 5 treatment groups 1 day later, as follows: group A, tafenoquine, 300 mg q.d. for 7 days (total dose, 2100 mg); group B, tafenoquine, 600 mg q.d. for 3 days (total dose, 1800 mg); group C, tafenoquine, 600 mg as a single dose; group D, no further treatment; and group E, primaquine, 15 mg q.d. for 14 days. On the day that chloroquine therapy was completed, parasitemia clearance was documented by 2 consecutive negative results of blood smears. Tafenoquine and primaquine were administered within 1 h of a meal under direct observation.

**Drug Sources**

The tafenoquine formulation (8-[(4-amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5(3-trifluoromethyl phenox) quinoline, succinate) consisted of unmarked gelatin capsules containing WR238605 succinate (100 mg base; bottle number/bulk, 69897; lot number, 08910496) produced under Good Manufacturing Practices at the University of Iowa College of Pharmacy (Iowa City). Chloroquine phosphate tablets (US Pharmacopeia; 500-mg salt formation equals 300-mg base formulation; Sterling Winthrop Company), and primaquine phosphate tablets (US Pharmacopeia; 26.3-mg salt formulation equals 15-mg base formulation; Sterling Winthrop Company) were obtained from the Walter Reed Army Medical Center pharmacy (Washington, DC).

**Randomization**

A computer-generated blocked randomization list (block size, 5) was used to assign patients sequentially to treatment groups. The randomization list was kept by an off-site investigator (D.S.W.) who was not directly involved with patient enrollment. To minimize losses between time of assigned treatment (randomization) and the beginning of drug treatment (prophylaxis, day 0), randomization was made as close to the end of the chloroquine treatment period as possible (day –1). Because of time constraints that were estimated to limit enrollment to ∼70 patients, a ratio of 1.5:1 for the 3 tafenoquine groups (≥15 subjects per group) and the 2 comparator groups (≥10 subjects...
per group) was selected to provide a useful balance by assigning most patients to the tafenoquine treatment groups, but also by including a sufficient number of subjects in the 2 comparator arms, to reliably depict the relapsing nature of \textit{P. vivax} malaria in Thailand, including some patients who were treated with low-dose primaquine. To achieve these target sample sizes, some assignments were eliminated (6 group D, 4 group E) as the trial progressed (nonrandomly). In each case, the patient was assigned the next treatment on the randomization schedule. For 2 enrolled subjects, treatment substitutions were made (one subject was moved from group E to group B to replace a patient in group B who dropped out of the study on the day that prophylaxis began, and the other was moved from group E to group D because of an inability to remain hospitalized for 14 days). In all cases, elimination of a group D or E assignment or substitution was made without the knowledge of the next treatment assignment or the identity of the next patient to be randomized.

**Procedures**

Microscopic examination of blood smears was conducted by a standard operating procedure whereby 200 oil-immersion fields (magnification, \times 1000) were read on Giemsa-stained thick blood smears by 2 independent readers who were blinded to the patient’s group assignment. The identification of \textgreater 1 asexual \textit{P. vivax} parasite was recorded as a positive smear result. For positive smear results, speciation was determined by examination of thin smears. Any discrepancies were resolved by a third senior study microscopist.

**Outcome Measurements**

**Efficacy.** The primary efficacy end point was the occurrence of microscopically proven \textit{P. vivax} malaria after treatment. Protocol follow-up for efficacy was for a minimum of 8 weeks, with additional follow-up to a total of 24 weeks. Follow-up time was measured from the time of receipt of the first dose of tafenoquine or primaquine terminal prophylaxis (day 0) to the date of relapse (drug failure), removal from the study (non-malaria related), loss to follow-up, or study completion.

**Safety and tolerability.** Patients were assessed daily during chloroquine and prophylaxis treatments. Assessments included a review of symptoms for adverse events (AEs) and malaria blood smear. Thereafter, evaluations were conducted at least every 2 weeks to week 8, and then every 2–4 weeks for up to 24 weeks. A complete blood cell count was determined and standard hepatic and renal function tests were conducted approximately every other day during treatment, and then every 2–4 weeks for up to 24 weeks. Methemoglobin levels were measured on a similar schedule using an OSM-3 Hemoximeter (Radiometer). Serum pregnancy tests were repeated monthly for women.

**Drug analysis.** Plasma samples were collected from tafenoquine recipients (groups A–C) according to a schedule designed for population pharmacokinetics and were measured for tafenoquine concentrations by an established high-pressure liquid chromatography method [14].

**Data management and statistical analysis.** Data were recorded on standardized case report forms, entered into a computerized database, and cross-checked for agreement. All randomized patients (n = 80) were included for analysis of efficacy (to time of relapse or loss to follow-up), toxicity, and tolerability. No patient was removed from the study if still available for follow-up, and all outcomes were included for analysis, regardless of compliance with dosing regimens (intent-to-treat). The per-protocol population included subjects who completed \geq 8 weeks of follow-up (n = 68).

Relapse rates (incidence density) were calculated as the number of patients who had relapse divided by the total number of person-years of follow-up. The primary estimate of efficacy of chloroquine plus tafenoquine, relative to chloroquine alone or chloroquine plus primaquine, was defined as the percentage reduction in the relapse incidence (density) rates. Corresponding confidence intervals based on the ratio of 2 Poisson variables were calculated using the exact conditional distribution [15]. The proportions of relapsed patients with \geq 8 weeks of follow-up (per-protocol population) were compared using Fisher’s exact test [16]. All reported CIs were 95%, and all P values were 2-sided. The Kaplan-Meier method was used to estimate the cumulative risk of relapse (and the SE) during follow-up, and cumulative relapse (survival) curves were compared using the log rank test [17]. Data from after the 6-month protocol follow-up period (i.e., the closing date) were excluded from analysis. Plasma tafenoquine concentrations were assessed for peak levels in each treatment group.

Reported AEs in the treatment groups were compared in terms of (1) the proportion of all randomized subjects with any (each) AE, and (2) the corresponding incidence rates (to number of AEs/total follow-up time). AEs reported on the day that a slide was found to be positive for malaria were discounted. The study was not designed to precisely estimate AE rates of low incidence or to detect differences among the treatment groups.

**RESULTS**

**Enrollments and withdrawals.** Eighty \textit{P. vivax}–infected patients met the eligibility requirements and were randomized to 1 of 5 treatment groups (figure 1 and table 1). One patient was not included because of G-6PD deficiency. All but 1 patient (in group B) randomized to receive tafenoquine or primaquine received all prescribed doses. There were no positive pregnancy test results during the study. Forty-six (83%) of 55 tafenoquine recipients, 10 (77%) of 13 recipients of chloroquine only, and
Figure 1. Patient flow diagram for a study of prophylactic treatment for relapse of Plasmodium vivax malaria. CQ, chloroquine; G-6PD, glucose-6-phosphate dehydrogenase; PQ, primaquine; TQ, tafenoquine.

The cumulative risk of relapse is summarized in figure 2. Compared with recipients of chloroquine plus primaquine, differences in cumulative risk were statistically significant for the 2 higher-dose regimens of chloroquine plus tafenoquine (i.e., those received by groups A and B; P = .04 and .048, respectively, by log-rank test), as well as for all recipients of chloroquine plus tafenoquine (n = 55; P = .004, by log-rank test). Compared with the chloroquine alone arm, the cumulative risk was lower for each chloroquine plus tafenoquine dose group (i.e., groups A–C; P < .001).

The patient in group C who experienced relapse vomited 1 h after tafenoquine administration and was not given another dose. Parasitemia was detected on a routine follow-up visit on day 112, and within several hours of detection, the patient became symptomatic. All patients who experienced relapse were treated with a blood schizonticidal dose of chloroquine and primaquine (15 mg q.d. for 14 days).

Safety and tolerability. With the exception of transient
Table 2. Protective efficacy of tafenoquine (TQ) against relapse of *Plasmodium vivax* malaria.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Regimen</td>
<td>TQ, 300 mg q.d. for 7 days</td>
</tr>
<tr>
<td>No. of randomized patients</td>
<td>18</td>
</tr>
<tr>
<td>Duration of follow-up, days</td>
<td>140.6</td>
</tr>
<tr>
<td>Mean</td>
<td>168</td>
</tr>
<tr>
<td>Median</td>
<td>2530</td>
</tr>
<tr>
<td>No. of relapses</td>
<td>0</td>
</tr>
<tr>
<td>No. of patients at riska</td>
<td>15</td>
</tr>
<tr>
<td>Rate</td>
<td>0/15</td>
</tr>
<tr>
<td>Compared with group D</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Compared with group E</td>
<td>.15</td>
</tr>
<tr>
<td>Relapses per person-year</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE. CQ, chloroquine; PQ, primaquine.

*a* For persons who were in follow-up (i.e., at risk) for >2 months. Data are no. of relapses per no. of persons at risk for >2 months.

*b* Determined by Fisher’s exact test.

*c* Percentage reduction in the incidence (density) rate, compared with CQ alone or PQ.

*d* Conditional exact 95% CI and test for ratio of 2 Poisson variables.

Elevations in the methemoglobin level (figure 3), there were no clinically important laboratory values in tafenoquine or primaquine recipients. Peak mean levels of methemoglobin in the tafenoquine groups (up to 12% in group A and 3.3% in the primaquine group) were not associated with any symptoms attributable to elevated methemoglobin levels [18].

AEs among the treatment groups during chloroquine treatment, during prophylaxis (tafenoquine or primaquine), and
after prophylaxis were mild and transient, consisting predominantly of weakness, headache, vertigo, loose stools or diarrhea, nausea, and abdominal discomfort. During chloroquine treatment, all patients had ≥1 AE, with neurological complaints (vertigo or headache) in nearly all subjects and gastrointestinal disturbances in approximately one-half of subjects. During tafenoquine and primaquine prophylaxis, rates for any AE were similar among the tafenoquine and primaquine groups, but a higher proportion of gastrointestinal disturbances (abdominal discomfort or diarrhea) was reported among tafenoquine recipients than among primaquine recipients (table 3). After tafenoquine and primaquine therapy, approximately one-half of the tafenoquine recipients had ≥1 AE (primarily headache or vertigo), whereas the primaquine recipients reported none. There were no serious or life-threatening AEs.

**Drug concentrations.** In groups A and B, individual peak tafenoquine concentrations ranged from 710 to 1710 ng/mL and from 782 to 1843 ng/mL, respectively (data not shown). Figure 4 shows that the lone patient in group C who experienced relapse had a peak tafenoquine level of 276 ng/mL, whereas the minimum peak level in nonrelapsing group C patients was 432 ng/mL.

**DISCUSSION**

The findings in this study strengthen the evidence that tafenoquine is a safe and effective radical cure for *P. vivax* malaria in Thailand. Of note, our data suggest that even a single 600-mg dose of tafenoquine may be effective in preventing relapse of *P. vivax* malaria, commensurate with the previous dose-ranging study in which a single 500-mg dose prevented relapse in 6 of 7 patients who were observed for 2–6 months [6]. Equally encouraging was that 600 mg of tafenoquine—the largest daily dose amount ever administered for radical cure of *P. vivax* malaria—was safe and well tolerated. Unlike the previous dose-ranging study, however, in which at least 1 of the 2 relapses among 23 tafenoquine recipients may have been associated with an 8-aminoquinoline–tolerant infection [6], a more likely explanation for the relapse in the patient in the single-dose tafenoquine group in this study was vomiting soon after dosing, resulting in subtherapeutic blood levels [4]; indeed, this patient recorded the lowest peak tafenoquine plasma level of all tafenoquine recipients, at 276 ng/mL, whereas the minimum peak concentration of all nonrelapsing tafenoquine recipients was 432 ng/mL, and it was 323 ng/mL in the previous dose-ranging study [6] (D.S.W., unpublished data).

The 25% failure rate in the primaquine comparators correlates with a report indicating that a minority of *P. vivax* infections in Thailand will be refractory to primaquine at a dosage of 15 mg per day for 14 days [3] but with far better responses using a dosage of 22.5 mg for 14 days [19]. Indeed, had this study included a 22.5-mg primaquine group, we predict that there would have been fewer relapses in the prima-
Tafenoquine to Prevent *P. vivax* Relapse

**Table 3.** Adverse events (AEs) in recipients of tafenoquine (TQ) or primaquine (PQ) therapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>A (n = 18)</th>
<th>B (n = 19)</th>
<th>C (n = 18)</th>
<th>A–C (n = 55)</th>
<th>E (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>TQ, 300 mg q.d. for 7 days</td>
<td>TQ, 600 mg q.d. for 3 days</td>
<td>TQ, 600 mg as a single dose</td>
<td>...</td>
<td>PQ, 15 mg q.d. for 14 days</td>
</tr>
<tr>
<td>Study days b</td>
<td>1–7</td>
<td>1–3</td>
<td>1</td>
<td>...</td>
<td>1–14</td>
</tr>
<tr>
<td>Any AE</td>
<td>13 (72)</td>
<td>14 (74)</td>
<td>8 (44)</td>
<td>35 (64)</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Any GI AE c</td>
<td>4 (22)</td>
<td>3 (16)</td>
<td>2 (11)</td>
<td>9 (16)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Any neurological AE d</td>
<td>8 (44)</td>
<td>8 (42)</td>
<td>4 (22)</td>
<td>20 (36)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>AE experienced</td>
<td>Abdominal pain</td>
<td>3 (17)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>4 (7)</td>
</tr>
<tr>
<td></td>
<td>Anorexia</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>1 (6)</td>
<td>3 (16)</td>
<td>1 (6)</td>
<td>5 (9)</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>1 (6)</td>
<td>3 (16)</td>
<td>1 (6)</td>
<td>5 (9)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Vertigo</td>
<td>8 (44)</td>
<td>8 (42)</td>
<td>4 (22)</td>
<td>20 (36)</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>1 (2)</td>
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<tr>
<td></td>
<td>Headache</td>
<td>4 (22)</td>
<td>4 (21)</td>
<td>2 (11)</td>
<td>10 (18)</td>
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<tr>
<td></td>
<td>Myalgia</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Rash/pruritus</td>
<td>2 (11)</td>
<td>1 (5)</td>
<td>1 (6)</td>
<td>4 (7)</td>
</tr>
<tr>
<td></td>
<td>Weakness</td>
<td>8 (44)</td>
<td>10 (53)</td>
<td>4 (22)</td>
<td>22 (40)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. GI, gastrointestinal.

a All patients received chloroquine (1500 mg over 3 days) prior to TQ or PQ administration.
b TQ and PQ dosing started on study day 0, and AE collection started on study day 1. AE collection occurred only during prophylaxis administration.
c GI events included abdominal pain, anorexia, diarrhea, nausea, and vomiting.
d Includes vertigo or headache only.

**quine group.** In some areas of endemicity, but not Thailand, *P. vivax* demonstrates strong regional primaquine tolerance patterns, as reflected when 14 days of primaquine therapy failed to prevent *P. vivax* malaria in 6 (2.8%) of 214 Australian army troops returning from Papua New Guinea [20]. Tafenoquine therapy failed in 7 (1.9%) of the 378 soldiers as well, but it is unknown whether this was related to 8-aminoquinolone cross-tolerance. Chloroquine-resistant *P. vivax*, which is typically suspected when parasitemia reappears within 30 days of chloroquine treatment, has not been reported in Thailand and was not considered to be a factor in this study [3, 21].

The effectiveness of tafenoquine over 3 dose regimens, with total doses ranging from 600 mg to 2100 mg administered over 1–7 days, underscores a large degree of flexibility in dosing. To improve convenience over the previous dose-ranging study, we eliminated the split-dose regimen (3 consecutive days per week for 2 weeks) and began tafenoquine administration the day after completion of the chloroquine regimen, 1 day sooner than in the previous *P. vivax* infection radical cure study [6], without any untoward clinical effects. Compared with primaquine for radical cure in Thailand, where it is typically administered for ≥14 days at daily doses of 15–22.5 mg [1, 2, 19], single- or multiple-day dosing regimens with tafenoquine could improve radical cure compliance and thus reduce relapse rates. Taken together, the results of this study and the previous dose-ranging study indicate that a 3-day regimen of tafenoquine (600 mg q.d.) might provide a desirable balance of efficacy, tolerability, and convenience for the radical cure of *P. vivax* malaria in Thailand.

AEs associated with tafenoquine therapy are generally mild and transient, consisting predominately of headache and gastrointestinal symptoms, including nausea, bloating, vomiting, and diarrhea [6, 8, 9]. Like our previous study, tafenoquine was administered soon after a meal to improve gastrointestinal tolerance as well as bio-availability [6]. Nonetheless, gastrointestinal AEs were observed more frequently among tafenoquine recipients than primaquine recipients during the dosing period. Tafenoquine, like other 8-aminoquinolines, also causes transient, mild elevations in methemoglobin concentrations. In our study, methemoglobin levels generally correlated with dose amounts, but all patients remained asymptomatic. In general, methemoglobin concentrations of 10%–25% produce asymptomatic cyanosis, whereas levels of 35%–40% may cause dyspnea on exertion, headaches, and fatigue [18]. Of importance, tafenoquine is contraindicated in persons with G-6PD deficiency because of potentially serious hemolysis, as well as in pregnant women in the event of fetal G6-PD deficiency [22, 23]. Accordingly, all potential recipients of tafenoquine require...
G-6PD screening, and women of childbearing potential should undergo pregnancy testing. Despite these handicaps, tafenoquine’s role in the radical cure of \textit{P. vivax} malaria deserves further evaluation, including evaluation of simultaneous administration of chloroquine and tafenoquine.

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