PRIMAQUINE: REPORT FROM CDC EXPERT MEETING ON MALARIA CHEMOPROPHYLAXIS I

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Abstract. Primaquine phosphate has been used for preventing relapse of *Plasmodium vivax* and *P. ovale* malaria since the early 1950s, based on its ability to kill latent (hypnozoite) and developing liver stages of these parasites. There are three uses for primaquine in malaria: radical cure of established infection with *P. vivax* or *P. ovale* malaria; presumptive anti-relapse therapy (PART; terminal prophylaxis) in persons with extensive exposure to these parasites; and primary prophylaxis against all malaria species. All persons for whom primaquine is being considered must have a glucose-6-phosphate dehydrogenase (G6PD) enzyme level checked before use, and persons who have a deficiency of G6PD must not take primaquine for prophylaxis or PART. The recommended adult dose for PART based on clinical trials and expert opinion is 30 mg base daily for 14 days, started on return from a malarious region and overlapping with a blood schizonticide. The adult dose for primary prophylaxis is 30 mg daily begun 1 day before travel and continued for 7 days after return. This review will examine the evidence for these recommendations.

SUMMARY

Indications. Presumptive anti-relapse therapy (terminal prophylaxis) in persons heavily exposed to *Plasmodium vivax* or *P. ovale*.

Prophylaxis (causal), as a second line agent, for prevention of all *Plasmodium* species (not currently Food and Drug Administration [FDA]-approved for this indication).

Radical cure in persons with a confirmed bloodstream infection with *P. vivax* or *P. ovale*.

Dosing. Note: 15 mg base = 26.3 mg of the phosphate salt; doses for all anti-malarials in this document are expressed in the base form. Glucose-6-phosphate dehydrogenase (G6PD) testing must be performed before a patient takes primaquine.

Adult. Presumptive anti-relapse therapy: 30 mg daily for 14 days, based on clinical trials data (A-II†) and current expert opinion (C-III).‡ Dosing should overlap with a blood schizonticide.

Prophylaxis: 30 mg daily started 1 day before travel, taken daily during travel and for 7 days after travel (A-I).

Radical cure: 30 mg daily for 14 days to overlap with the blood schizonticide agent (A-I).

Pediatric. Presumptive anti-relapse therapy: 0.5 mg/kg (up to a maximum of 30 mg) daily for 14 days (B-III).

Prophylaxis: 0.5 mg/kg daily (up to a maximum 30 mg) started 1 day before travel, taken daily during travel and for 7 days after travel (B-I for use in children 7 years of age and older; B-III for use in children 6 years of age and younger).

Radical cure: 0.5 mg/kg daily (up to a maximum 30 mg) for 14 days to overlap with the blood schizonticide agent (A-I).

Efficacy. Presumptive anti-relapse therapy: high (~95% and greater) at doses of 30 mg daily for 14 days (in combination with a blood schizonticide such as chloroquine). Although 15 mg daily (0.25 mg/kg/d) for 14 days effectively prevents relapse with *P. vivax* from many areas of the world,

some strains of *P. vivax* (principally found in Southeast Asia and South Pacific) may not be eradicated at this dosage.

Prophylaxis: clinical trials indicate > 85% protective efficacy against *P. falciparum* and primary *P. vivax* infections at a dose of 30 mg daily.

Radical cure: high (> 90%) with medication compliance and 30 mg daily equivalent dosing.

Adverse drug reactions. Most common mild/moderate adverse drug reactions (ADRs)Δ: abdominal pain, nausea, vomiting.

Severeδ: hemolysis in persons with G6PD deficiency. Methemoglobinemia occurs, but is not reported to be clinically significant at dosages used for prophylaxis. In studies, 0–2% of persons have reported a severe reaction and 0–2% have discontinued prophylaxis because of ADRs.

Contraindications.
- G6PD deficiency
- NADH methemoglobin reductase deficiency
- Known hypersensitivity to primaquine or related drugs (e.g., iodoquinol)
- Persons receiving treatment with other potentially hemolytic drugs
- Pregnancy (even if a pregnant woman is G6PD normal, the fetus may not be)
- The packaging label states that primaquine is contraindicated in persons with illnesses manifest by a tendency to granulocytopenia (lupus erythematosus and rheumatoid arthritis), but data are lacking on this association at dosages used in malaria chemoprophylaxis.

Precautions. Must have G6PD testing performed before using primaquine.

Drug interactions. Primaquine 30 mg/day has caused severe methemoglobinemia in HIV-infected individuals when used for prophylaxis of *Pneumocystis jiroveci* (previously *P. carinii*) pneumonia, especially in those currently or recently taking dapsone.

Use during pregnancy. Contraindicated.

Use during breastfeeding. Use only if infant is tested for G6PD deficiency and has normal enzyme levels.

Use in children. May be used in children of any age.

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† Infectious Diseases Society of America-United States Public Health Service Grading System for ranking recommendations in clinical guidelines.[1] Strength of recommendation: A, good evidence to support a recommendation for use; B, moderate evidence to support a recommendation for use; C, poor evidence to support a recommendation; D, moderate evidence to support a recommendation against use; E, good evidence to support a recommendation against use. Quality of evidence: I, evidence from one or more properly randomized, controlled trials; II, evidence from one or more well-designed clinical trials, without randomization; from cohort or case-controlled analytic studies (preferably from > 1 center); from multiple time-series; or from dramatic results from uncontrolled experiments; III, evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

‡ 15 mg daily for 14 days is the current FDA-approved regimen; 30 mg daily for 14 days is not currently an FDA-approved regimen, although clinical trials data (A-II) and current expert opinion (C-III) support the use of the higher dose.

Δ Mild/moderate ADRs enumerated if reported in at least two studies at > 2% frequency; ordered according to number of studies that reported this ADR.

δ Severe ADRs may be defined in various ways in different studies, but include ADRs interfering with activities of daily living or prompting the seeking of medical attention. Severe ADRs may also include any of the reactions listed under mild to moderate ADRs if they are severe in intensity.

INTRODUCTION

Since its approval in 1952 by the FDA, primaquine has been the only available agent capable of preventing relapse after infection with *Plasmodium vivax* and *P. ovale* malaria species. This has been termed radical cure. Primaquine, an 8-aminoquinoline, kills latent (hypnozoite) and developing liver stages of these plasmodia. At therapeutic doses, primaquine also exerts lethal activity against the asexual blood stages of *P. vivax* but not those of *P. falciparum*.[2–4] When primaquine is given presumptively in conjunction with a blood stage prophylaxis agent to an individual who has traveled to an area of the world where *P. vivax* or *P. ovale* occurs, therapy is called terminal prophylaxis or "presumptive anti-relapse therapy" (PART). PART is a term that more accurately defines its role and is the term that will be used. Some health authorities recommend that PART be administered to individuals after substantial risk of infection with *P. vivax* or *P. ovale*,[5,6] although a consensus defining "substantial" risk is lacking.

Primaquine may also be used as a "primary" prophylactic because it prevents primary parasitemia by all species of malaria by destroying these parasites in the liver before they reach the bloodstream and cause disease.[7] Prophylactic agents that prevent the blood stage infection by killing developing liver stage parasites are referred to as "causal" prophylactics. Primaquine may cause lethal hemolysis when administered to individuals deficient in G6PD. All persons who receive primaquine are required to have testing for G6PD. Primaquine should not be administered for prophylaxis in individuals deficient in G6PD.

Primaquine's mechanism of action is poorly understood, but it severely disrupts the metabolic processes of plasmodial mitochondria. The anti-malarial activity is probably attributable to interference with the function of ubiquinone as an electron carrier in the respiratory chain. Another potential mechanism of action against plasmodia is the production of highly reactive metabolites that generate toxic intracellular oxidative potentials.

RECOMMENDED USES AND DOSING OF PRIMAQUINE

There are three uses for primaquine in malaria: prophylaxis, presumptive anti-relapse therapy (terminal prophylaxis) for *P. vivax* and *P. ovale*, and radical cure after *P. vivax* or *P. ovale* clinical disease. The focus of this review is the use of primaquine for prophylaxis and PART. Note: 15 mg base = 26.3 mg of the phosphate salt; doses for all anti-malarials in this document are expressed in the base form. G6PD testing must be performed before prescribing primaquine.

Prophylaxis. Prophylaxis prevents primary parasitemia (as opposed to PART that is used to prevent relapse of *P. vivax* and *P. ovale* by killing hypnozoites). When primaquine is used as prophylaxis, a dose of 30 mg daily (adult dose) beginning 1 day before exposure and continuing for 1 week after departure from an area with malaria is recommended.[5–7] For adults < 60 kg and children, the Centers for Disease Control and Prevention (CDC)-recommended dosage is 0.5 mg/kg/d (to a maximum daily dose of 30 mg).[5]

PART (terminal prophylaxis). PART constitutes presumptive therapy to prevent relapse by *P. vivax* and *P. ovale* by killing liver stage hypnozoites. For both historical and safety considerations in the era before G6PD testing was available, the current FDA-approved dose is 15 mg daily for 14 days. However, *P. vivax* strains acquired in Papua (Indonesian New Guinea), areas of Oceania, and some other parts of the world require a higher dose of primaquine to prevent relapse. To achieve reliable eradication of parasites and with G6PD testing available, the CDC has recommended an increase in dose from 15 to 30 mg daily for 14 days for adults.[5] Expert opinion and clinical trials data support this recommendation although clinicians should be aware that the 30-mg daily dose is not FDA approved. The pediatric dose has also been increased from 0.25 to 0.5 mg/kg once daily (to a maximum of 30 mg). To decrease the risk of clinical failure in individuals weighing > 70 kg, the duration of treatment with 30 mg daily can be extended to achieve a total dose of 6 mg/kg, especially if the infection was acquired in an area of known tolerance to standard primaquine therapy.

Dosing should coincide with the last 2 weeks of chloroquine, mefloquine, or doxycycline prophylaxis or initiated during the final week of atovaquone-proguanil prophylaxis.

Radical cure. Primaquine used in conjunction with an effective blood stage schizonticide, such as chloroquine, for the treatment of a symptomatic patient with *P. vivax* or *P. ovale* malaria is termed radical cure. Used in this way, primaquine will prevent relapse from dormant liver stage or hypnozoite forms of *P. vivax* and *P. ovale* parasites. The doses of primaquine are the same as for PART above. If the results of G6PD testing return in time and the patient is found to be

TABLE 1
Efficacy of primaquine for primary prophylaxis

Country/population	Study type	Dosage/sample size (n)	Duration of prophylaxis	Efficacy (95% CI)
USA/American volunteers[10]	Experimental challenge	15 mg/d (n = 3) 30 mg/d (n = 3) 45 mg/d (n = 1)	6 days after experimental infection	*P. falciparum* infection in: 1/3 on 15 mg/d 0/3 on 30 mg/d 0/1 on 45 mg/d
USA/American volunteers[2]	Experimental challenge	10 mg/d (n = 10) 15 mg/d (n = 10) 30 mg/d (n = 10)	6 days after experimental infection	*P. vivax* infection in: 3/10 on 10 mg/d 2/10 on 15 mg/d 0/10 on 30 mg/d
USA/American volunteers[8]	Experimental challenge	30 mg/d (n = 5)	6 days following experimental infection	*P. falciparum* infection in: 0/5 on 30 mg/d
Papua (Indonesian New Guinea)/ non-immune migrants[16]	Randomized, open label placebo-controlled trial	30 mg/d (n = 97)	20 weeks	93% overall (71%–98%) 88% *P. falciparum* (48%–97%) 92% *P. vivax* (37%–99%)
Papua/non-immune migrants[12]	Non-randomized open label	30 mg every other day (n = 54)	16–19 weeks	74% *P. falciparum* 90% *P. vivax*
Kenya/children[11]	Randomized, placebo-controlled, double-blind	a. 0.5 mg/kg 3 d/week (n = 40) b. 0.5 mg/kg/d (n = 32)	11 weeks 11 weeks	0% efficacy against *P. falciparum* 85% (68%–93%) *P. falciparum* parasitemia; 83% (50%–94%) *P. falciparum* clinical malaria
Papua/non-immune migrants[13]	Randomized, placebo-controlled, double-blind	30 mg/d (n = 126)	52 weeks	94.5% (57%–99%) *P. falciparum* 90.4% (58%–98%) *P. vivax*
Colombia/non-immune soldiers[14]	Randomized, placebo-controlled, double-blind	30 mg/d (n = 122)	16 weeks	94% (78%–99%) *P. falciparum* 85% (57%–95%) *P. vivax*. (note: counted symptomatic malaria cases only, not all parasitemias)
Ethiopia/Israeli travelers[19]	Prospective observational	15–30 mg/d (n = 106)	2–3 weeks	5.7% infected with malaria; 4 *P. falciparum*, 1 *P. vivax*, 1 both

G6PD normal, primaquine should be initiated to overlap with some portion of the blood stage treatment of these species.

EFFICACY AND EFFECTIVENESS

Prophylaxis (Table 1). In clinical studies using experimental challenge with infectious sporozoites, the timing of primaquine dosing proved critical to protective efficacy. Single doses of 30 mg given during days 1 or 3 after sporozoite injection were effective in preventing malaria, but lower amounts of primaquine and any dose given before or after that window were not reliably effective[8] (although very high doses, e.g., 120–180 mg, were effective when given just before challenge).[9] Similarly, a single 45-mg dose given alone or with chloroquine before or on the day of experimental challenge with *P. falciparum* did not have a causal prophylactic effect.[10] For daily dosing regimens, early studies showed less than optimal efficacy at 15 mg/d, whereas 30 mg/d provided good efficacy.[2,8,10]

More recently, a thrice weekly regimen of 15 mg primaquine in Kenyan children showed no protective efficacy against *P. falciparum*,[11] and an alternate day regimen of 0.5 mg/kg in Indonesia proved 74% and 90% effective against *P. falciparum* and *P. vivax*, respectively.[12] All of these data point to an adult regimen of 30 mg daily for the prevention of malaria.

A number of studies conducted in the past 10 years examined daily primaquine (30 mg or an ~0.5-mg/kg dose in children) for primary prophylaxis in populations semi-immune and non-immune to malaria. A randomized, double-blinded placebo-controlled trial in Indonesian migrants to Papua reported protective efficacy of 95% (95% CI: 61–99%) against *P. falciparum* and 90% (95% CI: 65–99%) against *P. vivax*.[13] In a randomized, placebo-controlled trial among Kenyan children, 0.5 mg/kg/d was 85% (95% CI: 68–93%) effective for prevention of *P. falciparum* parasitemia.[11] In non-immune Colombian soldiers, a randomized, double-blinded placebo-controlled trial calculated protective efficacy at 94% (95% CI: 78–99%) for *P. falciparum* and 85% (95% CI: 57–95%) for *P. vivax*.[14] The authors of the Colombian study later combined chloroquine 300 mg weekly with daily primaquine (30 mg/d) to "improve the efficacy of primaquine for malaria prophylaxis."[15] However, protective efficacy for the combination was not appreciably improved: 88% (95% CI: 76–94%) effective (89% against *P. falciparum* and 88% against *P. vivax*).[15] Another randomized placebo-controlled trial in non-immune migrants to Papua showed protective efficacy of 93% (95% CI: 71–98%); 88% for *P. falciparum* and 92% for *P. vivax*.[16]

A limitation with each of these studies was the inability to continue follow-up after prophylaxis to look for late relapse (because the subjects lived in areas of high risk).[17] However, the early experimental trials did follow subjects for many months after challenge without evidence of relapse. Arnold and others[2] gave 30 mg of primaquine to volunteers on days −1, 0, and 1 though 6 after challenge with the Chesson strain of *P. vivax*. None of the 10 persons challenged developed *vivax* malaria when followed for a range of 190–450 days. This suggests that not only does primaquine have causal prophylactic activity, but that it will also prevent development of hypnozoites of *P. vivax*.

Although no severe falciparum malaria occurred among parasitemic subjects during the evaluation of primaquine pro-

phylaxis, some authorities are concerned that severe *P. falciparum* malaria could occur if there is primaquine failure,[18] because of the lack of blood schizonticidal activity of the drug against falciparum parasites.

A study reported the effectiveness of daily 15 mg of primaquine (30 mg for those > 70 kg) for primary prophylaxis in non-immune Israeli travelers.[19] Primaquine was more effective than mefloquine or doxycycline in preventing malaria caused by *P. vivax*, with post-travel infection rates for all species of malaria 6%, 52%, and 53%, respectively. The mefloquine failures were all caused by late occurrences of *P. vivax*, and in the doxycycline group, no travelers completed the post-travel 4-week course.

Prophylaxis is not currently included as an approved labeled use of primaquine. Nonetheless, the drug offers important advantages to travelers departing on short notice or for travel that has only a brief risk (given its relatively short post-travel dosing). Unfortunately, obtaining confirmation of adequate G6PD levels in individuals before prescribing primaquine requires phlebotomy and can take up to 1 week or longer. Nevertheless, primaquine for prophylaxis in G6PD-normal, non-pregnant travelers can be recommended as an alternative when other chemoprophylactic agents are inappropriate or contraindicated.[5,6,20]

PART (terminal prophylaxis) and radical cure. Primaquine is usually used to prevent relapse of *P. vivax* or *P. ovale*, i.e., to kill developing or dormant liver stages of a confirmed infection (radical cure) or as presumptive therapy to prevent relapse of suspected or possible infection. The majority of *P. vivax* and *P. ovale* cases occur > 2 months after return from travel, even in persons who take appropriate malaria chemoprophylaxis,[21] and could be prevented by PART with primaquine. While there is reasonable consensus among experts that PART should be used in those with "intense" or "significant" exposure, there is no consensus as to what constitutes an intense or significant exposure. There is agreement that most travelers do not need PART because the overall risk of developing malaria caused by *P. vivax* or *P ovale* is low, and the requirement to screen for G6PD deficiency before prescribing primaquine makes its use impractical for many travelers. PART should be considered for persons who have resided for prolonged periods (e.g., 6 months or more) in high-risk areas or who experience intense exposure to *P. vivax* such as has been described in rafters on the Omo River in Ethiopia[19] or in travelers to Papua New Guinea.[22]

To put imported malaria into perspective, for the years 1998 through 2004, there were 9,491 cases of malaria reported in the United States;[23–29] 4,574 (48.2%) of these were caused by *P. falciparum*, 2,790 were caused by *P. vivax* (29.4%), 373 (3.9%) were caused by *P. malariae,* and 260 (2.7%) were caused by *P. ovale*. In the remaining cases, the species was not determined. Of these cases, there were 38 deaths attributable to *P. falciparum*, 1 to a mixed *P. falciparum*/*P. malariae* infection, 2 to *P. ovale*, 1 to *P. vivax*, and in 2 cases, the species could not be determined. The overall case fatality rate has been estimated by the CDC to be 0.06% for *P. vivax*, 0.3% for *P. ovale* and *P. malariae*, and 1.3% for *P. falciparum*.[30]

Until recently, the most widely accepted and FDA-approved regimen of primaquine in PART was 15 mg daily for 14 days.[31,32] An alternative regimen of 30 mg daily for 14 days had been used when so-called "tolerant" strains of *P. vivax* (mostly from Southeast Asia or Oceania) were suspected.[31] While certain strains of *P. vivax* have been termed primaquine-tolerant or -resistant (i.e., not eradicated by the 15-mg dose), it is more likely that these strains represent *a priori* biologic differences in sensitivity to primaquine rather than true development of tolerance or resistance to primaquine.

From the beginning of experimental work using the Chesson strain of *P. vivax* (isolated from an American soldier in New Guinea during the Second World War)[33] and the St. Elizabeth strain of *P. vivax* (from temperate United States), a marked difference in response to primaquine was observed.[34–36] For elimination of the Chesson strain, a dose of 22.5 to 30 mg/d of primaquine for 14 days was required; 15 mg/d was not effective.[34,37] However, 15 mg/d of primaquine for 14 days eliminated the St. Elizabeth strain and later the Korean strain in US service personnel during the Korean War, although treatment of the Korean strain was always combined with chloroquine.[35,36] The decision to use 15 mg/d for 14 days in the early 1950s was based on the need for a dose that could be given safely to returning Korean War African American soldiers. Individuals of African descent have a higher likelihood of G6PD deficiency than most groups of whites, although their G6PD impairment tends to be mild. With the finding that the hemolytic anemia induced by primaquine was usually dose dependent, 15 mg/d was chosen as a dose that could be given to all US service personnel without concern that there would life-threatening hemolysis in the African-American soldiers (see section on Safety/Tolerability).

FDA licensure of primaquine in 1952 was based on the need to prevent relapsing *P. vivax* malaria in returning Korean war veterans, the finding from clinical trials establishing that the 15-mg daily dose could be safely given without medical supervision to African Americans who might develop hemolytic anemia with higher doses of primaquine and the knowledge that 15 mg daily for 14 days was efficacious against Korean strains of *P. vivax*.[34,36,38,39] Therefore, safety concerns, rather than efficacy against all strains of *P. vivax*, led to the licensure of the 15 mg daily for a 14-day regimen.

It is important to recognize that chloroquine or quinine have been shown to be required for the therapeutic efficacy of primaquine for the eradication of the hypnozoite once it has been established.[37] In a remarkable series of experimental infections with the Chesson strain of *P. vivax*, 15 mg daily for 14 days of primaquine when given 2 days after completion of a curative course of quinine (a short-acting drug) for the initial blood stage infection led to a cure rate of only 21% (4/19; 15 relapsed between 32 and 92 days). When the same regimen of primaquine was given concurrently with quinine or chloroquine, cure was seen in 95% (18/19) and 74% (14/19), respectively. These data generated 50 years ago require additional investigation, but practically, primaquine may exert its beneficial effect for PART or radical cure when combined with a 4-amino-quinoline drug such as chloroquine. Importantly, the mass administration of primaquine to returning Korean War veterans during the 1951–1952 trans-Pacific crossings was always accompanied by chloroquine. At the time, the thinking was to give chloroquine for the residual blood stages and primaquine for the hypnozoite. Two drugs were being administered for two indications with no thought of potentiation or synergy. This potential for synergy has

never been studied for primaquine with mefloquine, doxycycline, or atovaquone/proguanil.

Failure of standard primaquine therapy (15 mg daily for 14 days) to prevent relapse has been reported from the Solomon Islands,[40–43] Southeast Asia,[44–48] Brazil,[49–51] Colombia,[52] Guyana,[53] Guatemala,[54] Somalia,[55] Ethiopia,[56,57] Afghanistan[58,59] and elsewhere.[22,60–64] Because supervised compliance was not confirmed in these studies, these reports may not all represent failures of the 15-mg/d regimen. As examples, among US troops in Somalia who took PART, 43% relapsed, but compliance was not supervised and was self-reported,[55] and in a cohort of US soldiers with *P. vivax* malaria from Afghanistan, only 38% were compliant with PART.[59] Although a study from the Solomon Islands found no relapse during 1 year of follow-up subsequent to treatment with either a 15- or 22.5-mg daily regimen of primaquine,[65] a regimen of 22.5 mg daily was superior to the 15-mg regimen in Thailand.[47] Based on these findings as well as detailed clinical studies of the Chesson strain of *P. vivax*, experts have recommended the 30-mg adult daily regimen for radical cure of *P. vivax* malaria acquired in Southeast Asia or Oceania.[48,66,67] Last, there was a higher risk of relapse after standard primaquine therapy (equivalent to 15 mg daily) among subjects weighing > 70 kg, and higher doses equivalent to the 30-mg daily regimen of primaquine have been recommended for such individuals.[51,56,68]

After assessment of these clinical studies and the historical findings of a variable response to the 15-mg daily dose, the CDC has now recommended that 30 mg/d for 14 days be the standard dose for PART and radical cure.[5] Because of the possibility of decreased effectiveness in persons > 70 kg because of sub-therapeutic dosing, clinicians can consider extending the duration of PART in these individuals beyond 14 days targeting a total dose of 6 mg/kg.[67] A daily dose of > 30 mg is not recommended because the safety of higher daily doses is not proven.

To avoid drug-induced hemolysis, a regimen of 45 mg weekly (adult dose) for 8 weeks has been considered when a person has partial G6PD deficiency.[40,69] Both the 45- and 30-mg regimens have proven to be effective treatment against strains of *P. vivax* that were not killed by standard therapeutic regimens.[18,34,42,70] The alternative dosing regimen of 45 mg primaquine once weekly combined with weekly chloroquine for 8 weeks was introduced in the early 1960s by the US military.[40] Weekly dosing made supervised therapy feasible and improved compliance over the standard primaquine regimen given daily for 14 days. Studies performed in persons known to be moderately G6PD-deficient showed that the 45-mg weekly dose could be given with acceptable toxicity, although the data is limited and clinically apparent hemolytic anemia was seen. These observations evolved to a recommendation that the weekly dosing could be given to those who are G6PD-deficient. However, this weekly dosing regimen is not FDA approved, the data to support efficacy are limited, and safety data in G6PD-deficient persons, especially in those who have other than the mild, A-phenotype, are not known. Primaquine for PART in a known G6PD-deficient individual is not recommended. Use of primaquine for radical cure in a known G6PD-deficient individual should be used only after a careful risk/benefit assessment and under strict medical supervision.

A shortened course of primaquine for radical cure would improve effectiveness (lower cost, greater availability, greater compliance).[71] Earlier non-controlled studies reported that primaquine 15 mg daily for 5 days was effective in preventing *P. vivax* relapse.[72–74] However, controlled studies have shown 15 mg daily for 5 days has no therapeutic efficacy and, therefore, this duration of treatment should not be used.[75–79]

If a dose of primaquine is missed during PART, the course should be continued until all doses are taken (B-III). Because total cumulative dose is important in determining efficacy of primaquine treatment,[68] it is not necessary to restart PART.

PHARMACOKINETICS

In five fasted, healthy volunteers who were given oral primaquine along with an intravenous dose of radiolabeled primaquine, absorption was nearly complete,[80,81] with a mean bioavailability of 96%.[80] Areas under the concentration curve after doses of 15, 30, and 45 mg were linear, suggesting first-order kinetics. The mean t_{max} was 3 ± 1 hours (2- to 3-hour range) in healthy volunteers given a 45-mg dose. The mean C_{max} in these subjects was 153 ± 24 ng/mL (range, 131–180 ng/mL). In Thai volunteers given a 14-day regimen of primaquine, there was no difference in t_{max} and C_{max} after the first and last doses.[82] Among Indian patients being treated for *P. vivax* malaria, the mean t_{max} and C_{max} were similar to values in healthy subjects.[83]

Primaquine is extensively distributed in tissues, with the mean apparent volume of distribution ranging from 200 to 300 L.[80,83,84] Unlike chloroquine, primaquine does not accumulate in red blood cells. In one study, the mean whole blood to plasma concentration ratio of primaquine was 0.81.[80] Primaquine binds preferentially to the acute phase reactant protein alpha-1-glycoprotein, and the amount of that protein in blood may alter the distribution of free primaquine.[85]

The metabolism of primaquine in humans and various animal systems has been reviewed.[86] In human microsomes *in vitro*, primaquine was metabolized primarily to carboxyprimaquine.[80,87,88] The time to peak carboxyprimaquine levels in plasma was 3–12 hours, with the C_{max} being 10 times higher than the parent compound. Carboxyprimaquine does not accumulate during 14 days of dosing. Primaquine is also metabolized to a number of other identified and unidentified metabolites that are detectable in urine and plasma. Only ~1–4% of primaquine is eliminated as parent compound in urine.[80,89]

Primaquine has been shown to decrease the clearance of antipyrene, resulting in an increase in its half-life.[90] Antipyrene is a general probe for the hepatic cytochrome P-450 (CYP).[91] If there is no change in antipyrene metabolism with the drug of interest, there are likely to be no significant CYP interactions. Recent studies show that primaquine induces the CYP 1A2 enzyme in both recombinant and microsomal *in vitro* systems.[87,92,93] This induction could decrease the plasma concentrations of drugs that are metabolized by CYP 1A2, with a potential for decreased efficacy.[94,95] Examples of commonly prescribed drugs that are metabolized by CYP 1A2 are tricyclic antidepressants; antipsychotics (e.g., clozapine and haloperidol); and benzodiazepines, caffeine, propranolol, theophylline, and warfarin (http://medicine.iupui.edu/flockhart/table.htm). The clinical significance of this potential interac-

tion is not known; however, prescribing primaquine for prophylaxis concurrently with drugs that are metabolized by CYP 1A2, warfarin should be undertaken with caution or avoided. Because there is no other drug for PART or radical cure, clinicians should weigh the risks and benefits of using primaquine. Mefloquine inhibits metabolism of primaquine (and *vice versa*) in an *in vitro* microsome system, but the clinical relevance of this interaction is not known.[96]

In healthy volunteers, the half-life (elimination) of primaquine was 7 ± 4 hours (2- to 12-hour range).[84] In another study, it was 6 ± 2 hours.[80] In healthy Thai volunteers, it was 4 ± 1 hours after a 14-day dosing.[82] Similar estimates were observed in patients with *P. vivax* malaria and in those with G6PD deficiency.[83]

Although liver or renal disease could theoretically delay metabolism or excretion of primaquine,[97] there are no data available to suggest optimal dosing adjustments in individuals with hepatic or renal dysfunction. Current recommendations are to not change dosing of primaquine in patients with renal insufficiency or renal failure.[98]

Virtually all pharmacokinetic studies of primaquine have been conducted on fasted human subjects. Little is known of the effect of food on primaquine, with the exception of the apparent ability of food to greatly diminish the risk of gastrointestinal upset. In an uncontrolled study involving subjects who were fed 15 minutes after primaquine dosing,[99] the C_{max} and area under the curve for primaquine were substantially higher in fed subjects compared with subjects with malaria or healthy Thai or white subjects. Randomized studies of primaquine pharmacokinetics in fed versus fasted subjects are needed. Nonetheless, most authorities recommend that primaquine be administered with food or after a meal to avoid gastrointestinal adverse events, especially abdominal cramps.[38,97,100]

COMPLIANCE

No published study has examined compliance with a daily regimen of primaquine for prophylaxis. Studies of suppressive prophylaxis using other anti-malarials reveal that individuals are frequently non-compliant with doses that should be taken after leaving the malarious area.[101–103] Full compliance with the 2-week regimen of PART with primaquine in repatriated military populations has ranged from 4% to 80%.[104–106] The requirement for only 1 week of post-exposure prophylaxis when primaquine is used for primary prophylaxis should improve patient compliance. Given the importance of dosing within 24–72 hours after challenge (described previously),[8] compliance with daily dosing of primaquine may prove an important determinant of effectiveness, especially in areas of very high risk.[107]

SAFETY/TOLERABILITY

The most serious adverse event linked to primaquine is an acute intravascular hemolysis in people having an inborn deficiency of G6PD.[108] The most common adverse event in G6PD-normal, non-pregnant individuals is gastrointestinal upset if primaquine is ingested on an empty stomach.[13] A mild, self-limited, and asymptomatic methemoglobinemia occurs in most people receiving primaquine. Clinical studies of subjects receiving therapeutic or prophylactic regimens do not corroborate early studies suggesting that primaquine causes cellular immune suppression and leucopenia.

G6PD deficiency. Primaquine causes hemolytic anemia in people with an inborn deficiency of G6PD. The severity of hemolytic anemia seems to be related to primaquine dosing and the variant of the G6PD enzyme, i.e., the degree of G6PD deficiency. More than 300 allelic variants are known. These are divided into classes based on level of residual enzyme activity in red blood cells.[108] The most common variant occurs in persons of African descent (A⁻) who have a mild impairment of G6PD activity (usually > 10% activity), and in whom primaquine causes a mild hemolytic anemia limited to senescent red blood cells.[109] Other ethnic groups, including whites and Asians, may have a more severe form of G6PD deficiency (typically < 10% residual activity) that can result in progressive, potentially fatal hemoglobinemia and hemoglobinuria after treatment with standard doses of primaquine.[97] Prevalence of G6PD deficiency is relatively common among Africans (1–20%) and typically rare in other ethnic groups (< 1%).

In persons with normal levels of G6PD, hemolysis is not observed. One study reported no noticeable hemolysis among Thai patients with normal levels of G6PD taking 22.5 mg of primaquine daily for 14 days.[47] The same was true among 99 G6PD-normal Javanese adults receiving 30 mg primaquine daily for 20 weeks.[16]

In persons with mild impairment of G6PD activity, hemolysis starts 3–4 days after the first dose of primaquine and lasts ~7 days. Recovery with reticulocytosis occurs even if 30 mg primaquine daily dosing is continued because reticulocytes and the remaining red cells are relatively resistant to primaquine-induced hemolysis.[40]

A 45-mg weekly dose of primaquine does not cause clinically significant hemolysis in people having the A⁻ variant, and this was the basis for developing the 45 mg/wk for 8 weeks regimen for prevention of relapse.[40] Eight subjects with the A⁻ variant were administered 45 mg weekly for 8 weeks and developed only mild, asymptomatic hemolysis (hemoglobin decrease range, 0.5–2.5 g/dL).[110]

Investigators in Burma treated 20 patients who were hemizygous for mild deficiency and 2 patients hemizygous for severe deficiency with either one dose of primaquine (45 mg; 9 patients with mild deficiency and 1 severe) or 45 mg of primaquine weekly for 8 weeks (11 mild deficiency and 1 severe).[69] Although the numbers were small, they found no significant change in methemoglobinemia compared with the patients with normal G6PD levels and no clinical signs of drug-induced hemolysis. In a clinical trial involving seven G6PD-deficient Thai soldiers (with variable residual enzyme activity), hemolysis after a single dose of 45 mg primaquine was mild and affected 8–18% of red cells.[111] However, severe hemolysis has been reported after the administration of a single 45-mg dose in whites[112] and in patients in Vanuatu with severe deficiency.[113]

The degree of hemolysis in other variants of G6PD exposed to standard primaquine therapy (15–30 mg daily) varies widely. In Burma, two healthy volunteers infused with G6PD-deficient red blood cells and given 15 mg daily for 14 days lost 34–48% of those cells.[114] Among 441 patients treated with primaquine (15 mg/d for 14 days) for *P. vivax* in Thailand, 13

were G6PD-deficient.[115] These patients developed only slightly lower hematocrits. Primaquine induced hemolysis in three other Thai subjects (29% residual activity in one and 2–10% in the other two), with their hematocrits decreasing by 9–13%.[116]

The Mediterranean B⁻ variant of G6PD deficiency occurs in individuals whose ethnic background includes ancestors from the Mediterranean basin or west Asia. Individuals with the B⁻ variant have minimal or no detectable residual G6PD enzyme activity.[97,117] Administration of primaquine to people with the B⁻ variant risks severe, potentially life-threatening hemolysis. A randomized, open-label trial in Malaysian Borneo compared chloroquine, chloroquine-primaquine, and pyrimethamine-sulfadoxine for treatment of individuals with acute malaria. Sixteen subjects with severe G6PD deficiency were unwittingly treated with chloroquine-primaquine (1.5 g chloroquine and 15 mg/d primaquine for 3 days for *P. falciparum* infection or for 14 days for *P. vivax* infection). Seven subjects experienced hemolytic anemia, and five of them required transfusion with one to two units of blood. Among the transfused subjects, two suffered renal failure, with one requiring peritoneal dialysis.[118] Severe hemolysis with renal failure requiring dialysis was reported in a Thai soldier after three 15-mg doses of primaquine.[119] Severe hemolysis occurred among G6PD-deficient Sardinians given a single dose of 30 mg primaquine.[120]

Because of the risk of hemolysis in G6PD-deficient individuals, laboratory determination of the patient's G6PD status must be performed before prescribing primaquine. This can be done with either a quantitative determination of the enzyme level or a qualitative screening test.[121] Quantitative assays will identify nearly all persons with a G6PD deficiency; however, they are more expensive to perform and are not necessary to obtain for the purposes of determining whether primaquine may be safely administered. Qualitative screening tests are sufficient to identify individuals with a G6PD deficiency with the following exceptions: recent hemolysis in a person with one of the milder G6PD deficiency variants and some women who are heterozygous for the gene and have mild deficiency. In cases of primaquine-induced hemolysis, older erythrocytes are selectively hemolyzed, leaving younger cells with near normal levels of G6PD.[108,121] Nevertheless, qualitative tests will identify persons who will be at risk from taking primaquine, and if the test is abnormal, the drug should not be used for prophylaxis.

Persons deficient in the enzyme NADH methemoglobin reductase are extremely sensitive to hemoglobin-oxidizing agents such as primaquine.[122,123] This enzymatic deficiency is much rarer than G6PD deficiency and is associated with methemoglobinemia.

Methemoglobinemia. Methemoglobinemia (> 1% methemoglobin) usually occurs with therapeutic or prophylactic dosing regimens. One study reported mean/maximum methemoglobin levels of 6%/9%, 10%/18%, and 11%/18% among persons receiving 15, 22.5, and 30 mg of primaquine, respectively, for 14 days.[38] Another study ($N = 30$) of primaquine (15 mg for 14 days) reported mean methemoglobin levels of 5.9% (range, 1.3–19.3%) at 14 days; there were no reported symptoms relating to the methemoglobinemia.[124] Two weeks after the last dose, the highest methemoglobin level (19.3%) decreased to 2.3%. In other studies, methemoglobin levels as high as 18% have been reported among persons taking 22.5

mg daily for 14 days,[125] and in persons in a 20-week trial, the highest methemoglobin level recorded on the last day of prophylaxis was 8.5%.[16] In this latter study, the authors determined that the risk of methemoglobinemia did not increase with the duration of administration of primaquine and that it resolved within 2 weeks after cessation of dosing.[16] Among persons taking 0.5 mg/kg/d (adult dose equivalent 30 mg/d) primaquine for 1 year, no negative impact on the complete blood count or renal or hepatic function was seen; methemoglobinemia levels at week 50 ranged from 1.4% to 13% (mean, 5.8%).[13]

Cyanosis can occur when the methemoglobin level exceeds 15–20 g/L of blood (~10% of the normal level of hemoglobin),[97] although cyanosis may be seen in fair-skinned persons at methemoglobin levels of < 6%.[122] The clinical use of specific methemoglobinemia percentages is unclear. In some studies, methemoglobinemia values of up to 20% are often asymptomatic[126] and may be well-tolerated up to levels of 25%.[97] Most authorities have argued that, whereas patients tolerate levels < 10% quite well, persons with levels of 20% are likely to be symptomatic. Others suspect that the presence or absence of symptoms depends not just on absolute percentage of methemoglobinemia, but also the rapidity with which methemoglobinemia occurs.[122]

Symptoms may develop at lower methemoglobin levels in persons with underlying pulmonary disease and limited pulmonary reserve.[127] No study has documented clinically apparent methemoglobinemia after therapeutic or prophylactic regimens of primaquine, except in patients having an inborn deficiency of methemoglobin reductase.[97,124] In summary, primaquine-induced methemoglobinemia, although almost universal with clinical doses, seems to be mild, self-limited, and tolerated without symptoms or signs of cyanosis in otherwise healthy people.

Gastrointestinal adverse events. The risk of ADRs with primaquine increases with increasing doses of the drug (Tables 2 and 3).[97] In a large study ($N = 699$) evaluating doses of 15 mg/d or less of primaquine in adults, ADRs occurred no more frequently than with placebo.[38] Among fasted persons receiving 22.5–30 mg/d, 10–12% reported mild to moderate abdominal cramps.[38] Individuals taking 120 mg daily reported moderate abdominal cramps and nausea.[34] Administration of 240 mg/d resulted in moderate to intolerably severe abdominal cramps.[34] These early investigators noted that the risk of gastrointestinal upset at any dose of primaquine essentially disappeared when the drug was administered with food.[38]

A randomized, double-blind placebo-controlled trial giving fed adult subjects 30 mg daily for 1 year found no difference in the number or type of complaints between subjects receiving primaquine compared with those receiving placebo.[13] Fed Kenyan children dosed with 15 mg daily for 11 weeks tolerated primaquine as well as placebo.[11] Primaquine (0.5 mg/kg dose) for 18–20 weeks given every other day with a snack resulted in fewer ADRs than weekly chloroquine 5 mg/kg (300 mg in an adult) among Javanese children and adults in Papua.[100] In another randomized, placebo-controlled trial in Indonesian adults, only headache, cough, and sore throat were reported significantly more frequently in recipients of primaquine compared with those taking placebo.[16] Among 122 Colombian soldiers, epigastric pain, abdominal pain, and other gastrointestinal symptoms occurred among nine recipients (7.4%) of primaquine (30 mg daily) compared with 1 of

TABLE 2
Severe ADRs associated with primaquine use

Study location/design	Duration of dosing	Dosing regimen	Number of severe ADRs/number at risk	Adverse event	Discontinued because of severe ADRs
USA/experimental challenge[34]	14 d	15–240 mg/d	–	Abdominal cramping	NA
USA/experimental challenge[38]	6–14 d	15–120 mg/d	0/89	None	None
USA/experimental challenge[67]	7 d	60 mg/d	1/11	Abdominal cramping, vomiting, cyanosis	SADR attributed to another substance in 1 subject
Papua/randomized placebo-controlled[16]	20 wk	30 mg/d	0/97	None	None
Papua/randomized double blind, placebo-controlled[13]	52 wk	30 mg/d	0/126	None	None
Kenya/randomized double-blind, placebo-controlled[11]	11 wk	15 mg/d	0/32	None	None
Colombia/randomized, double-blind, placebo-controlled[14]	16 wk	30 mg/d	3/122	Epigastric pain, vomiting, abdominal pain	3%
Ethiopia/prospective observational[19]	2–3 wk	15–30 mg/d	1/106	Nausea, vomiting	1%
Papua/open clinical trial[100]	16–19 wk	0.5 mg/kg every other day	0/45	None	None
Thailand/open randomized clinical trial[47]	14 d	15 or 22.5 mg/d	0/167	None	None
Colombia/randomized, double-blind placebo-controlled[14]	17 wk	Primaquine 30 mg/d + 300 mg chloroquine/wk	2/100	Vomiting	2%

ADRs, adverse drug reactions; NA, not available.

54 subjects receiving placebo (1.9%; P = not significant).[14] Taken with a snack or meal, daily primaquine for prophylaxis (0.5 mg/kg/d) seems to be as well tolerated as placebo.

Neuropsychiatric adverse events. Psychomotor effects have not been noted,[128] and neuropsychiatric changes seem to be rare, with only a single case report of depression and psychosis after primaquine use.[129]

Immune effects. Laboratory studies suggest that primaquine inhibits lymphocyte proliferative responses *in vitro*.[130,131] These findings served as the basis of warnings that primaquine therapy may be linked to clinically significant immunosuppression.[97] Although inhibition of lymphocyte proliferation has been observed *in vitro*,[132] *in vivo* studies in mice[133] and monkeys did not disclose similar findings.[132,134] Primaquine did not inhibit human natural killer cell toxicity *in vitro*.[135] Moreover, clinical studies do not corroborate immunosuppression by primaquine. In subjects receiving primaquine, Fryauff and others[136,137] showed normal to elevated cellular immune responses to tetanus toxin epitopes and humoral immune responses to tetanus-diphtheria vaccine. Repeated testing of lymphocyte function during a year-long chemoprophylaxis trial produced no evidence of immune suppression or disturbance induced by moderate or long-term daily primaquine.[138,139] Moreover, long-term use of primaquine did not effect intestinal helminth and protozoal parasite burdens.[140]

An early report linked neutropenia to a 2-week course of primaquine therapy (dose not stated) among patients with rheumatoid arthritis.[141] However, none of 338 men given 15–30 mg of primaquine daily for 14 days showed evidence of leucopenia; 6%, 21%, and 4% of subjects who received primaquine 15, 22.5, and 30 mg, respectively developed leukocytosis (10,000–17,000 WBC/mm³).[38] Other investigators have also observed leukocytosis[42] or no alteration in white cell counts.[39,142] High-dose primaquine (120–240 mg daily) has been associated with neutropenia.[34,38,142] Based on this information, some authors have advised against its use in persons being treated with myelosuppressive drugs or who suffer from concurrent conditions characterized by bone marrow depression.[97] However, more recent clinical trials using prolonged daily primaquine dosing that included monitoring of complete blood counts (as well as hepatic and renal function testing) showed no evidence of toxicity.[13,16]

CONTRAINDICATIONS

Primaquine is contraindicated for prophylaxis in all persons with G6PD deficiency and in pregnant women (because of the risk of acute hemolysis in the fetus with unknown G6PD status). The packaging label states that primaquine is also contraindicated in persons with illnesses manifest by a tendency to granulocytopenia, e.g., lupus erythematosus and rheumatoid arthritis (although the rationale for this warning is suspect; see discussion above). The label further warns against concurrent treatment with other potentially hemolytic drugs or depressants of the myeloid elements of the bone marrow.[143] The label warns that quinacrine hydrochloride potentiates the toxicity of primaquine, and these drugs should not be administered together.

Persons deficient in the enzyme NADH methemoglobin reductase are extremely sensitive to hemoglobin-oxidizing agents such as primaquine.[122,123] Individuals with minimal cardiopulmonary reserve may poorly tolerate the methemoglobinemia induced by primaquine. Persons allergic to iodoquinol, a chemically related 8-aminoquinolone, may be allergic to primaquine.[144]

DURATION OF USE

Few studies have examined the long-term use of primaquine for prophylaxis. One study reported administration of 0.5 mg/kg daily for 52 weeks with no long-term toxicity detected.[13] Similar results were reported in studies that evalu-

TABLE 3
Mild to moderate ADRs associated with primaquine use

Study location/design	Sample size dose duration	Most frequent ADRs	Comparator	ADR risk with primaquine use
USA/experimental challenge[34]	$N = 45$ 15–240 mg/d 1–14 d	Abdominal cramping, anorexia, nausea, vomiting	None	In fasted subjects, risk related to dose. In fed subjects, no GI complaints
USA/experimental challenge[38]	$N = 89$ 15–120 mg/d 6–14 d	Abdominal cramping: 15 mg—0% 22.5 mg—7% 30 mg—4% 60 mg—33% 120 mg—100%	None	In fasted subjects, risk related to dose
USA/experimental challenge[67]	$N = 11$ 60 mg/d 7 d	Nausea, abdominal cramping	None	2 subjects with moderate ADRs
Papua/randomized placebo-controlled[16]	$N = 97$ 30 mg/d 20 wk	Headache, abdominal pain, cough, nausea, dizziness	Placebo	None higher than placebo
Papua/randomized double-blind, placebo-controlled[13]	$N = 126$ 30 mg/d 52 wk	Headache, abdominal pain, URI symptoms, itching/rash, fatigue	Placebo	Cough and itch higher than placebo
Kenya/randomized double-blind, placebo-controlled[11]	$N = 32$ 15 mg/d 11 wk	Headache, abdominal pain, fever, nausea, diarrhea	Placebo, mefloquine, doxycycline, chloroquine + proguanil	None higher than placebo
Colombia/randomized, double-blind placebo-controlled[14]	$N = 122$ 30 mg/d 16 wk	Gastrointestinal	Placebo	7.5% primaquine vs. 2% placebo
Ethiopia/prospective observational[19]	$N = 106$ 30 mg/d 2–3 wk	Vomiting	Mefloquine, doxycycline	1 of 106 subjects discontinued primaquine secondary to vomiting. 1 of 19 taking doxycycline discontinued
Papua/open clinical trial[100]	$N = 45$ 0.5 mg/kg/every other day 16–19 weeks	Headache, fever, diarrhea, abdominal pain, vomiting	Chloroquine	None higher than that associated with chloroquine use
Thailand/open randomized clinical trial[47]	$N = 81$ (15 mg/day) $N = 86$ (22.5 mg/day) 14 d	Not reported	Not reported	None noted
Colombia/randomized, double-blind placebo-controlled[14]	$N = 100$ 30 mg/d (+300 mg chloroquine/wk) 17 wk	Gastrointestinal	Placebo	

ADRs, adverse drug reactions.

ated 11- and 20-week regimens of primaquine.[11,14,16,100] Two studies examined toxicity of 30 mg weekly to twice weekly for 9–12 months and found no evidence of long term toxicity.[2,38] No data are available on use of primaquine for > 1 year.

THERAPEUTIC INDEX/OVERDOSE

Primaquine has a chemotherapeutic index[1] of 10.[34] High doses, 60–240 mg/d, lead to toxic reactions including abdominal cramps, nausea, and headache, and are also associated with cyanosis from methemoglobinemia.[145]

DRUG INTERACTIONS

Some antipyretics, analgesics, and sulfonamides may precipitate hemolysis in G6PD-deficient persons and compound hemolysis induced by primaquine.[97,109,117] Methemoglobine-mia can be induced in HIV-infected individuals being treated for or prophylaxed against *Pneumocystis jiroveci* pneumonia with primaquine 30 mg/d, especially in those currently or recently taking dapsone.[127,146–149]

Primaquine can be administered with oral contraceptives with no apparent interaction or interference with hepatic metabolism of the contraceptives.[150] Clinical trials have shown that primaquine does not inhibit humoral or cellular immune responses after tetanus or tetanus/diphtheria vaccination.[136,137]

Quinacrine seems to potentiate the toxicity of anti-malarial agents that are structurally related to primaquine, and the concomitant use of quinacrine and primaquine is not recommended.[144,151]

SPECIAL POPULATIONS

The pharmacokinetics of primaquine have not been studied in children, pregnant women or patients with renal or hepatic dysfunction.[152]

Children. Although few studies document the safety and tolerability of primaquine in children, the drug has been used

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[1] Chemotherapeutic index is the ratio of the largest tolerated dose divided by the smallest effective dose (in this case the dose capable of preventing nearly all relapses).

TABLE 4
Cost of anti-malarial drugs

Regimen	Cost for 14-day stay including recommended pre- and post-travel doses*
Primaquine	$47.61
Chloroquine	$39.76
Doxycycline—generic	$11.00
Vibra-Tabs (Pfizer)	$142.28
Mefloquine	$84.64
Atovaquone/proguanil	$113.39

* Data taken from reference 170 with permission.

in children for > 50 years. Weiss and others[11] reported good tolerance with primaquine (0.5 mg/kg/d) for primary prophylaxis in Kenyan children 9–14 years of age. In another study of primary prophylaxis,[100] Baird and others included children as young as 7 years of age.

The lower age or weight limit of primaquine use has not been determined. Some public health authorities recommend that primaquine not be given to children < 4 years of age because of the risk of hemolysis,[153] and others recommend it not be used in children < 1 year old.[154,155] Some investigators avoid administering it to young children for radical cure of *P. vivax*.[156] In some malaria control programs, it is not used for children < 1 year of age[79,157] or for those < 3[158] or 6 months of age in other programs.[159,160] In Vanuatu, it is not given to children who weigh < 9 kg.[161] The American Academy of Pediatrics does not list a lower age limit for primaquine use,[162] nor do some other authors[163] and public health authorities.[5,6,164] Those who recommend against using primaquine in children do not cite data supporting their view. *In vitro* work does suggest, however, that neonatal erythrocytes may undergo endocytosis in response to primaquine (as well as to other drugs).[165,166]

In summary, limited data support the safety and efficacy of primaquine for primary prophylaxis in children 7 years of age and older. There is no evidence to suggest that children of any age who are not deficient in G6PD do not tolerate the drug, although data are lacking. Because the use of primaquine requires performance of a blood test to check G6PD level, and because of the requirement for daily administration of the drug, its use in small children may be problematic. There are other efficacious and better-studied drugs that can be administered to children to prevent malaria, including drugs that require once weekly administration and that do not require phlebotomy. Primaquine could, therefore, be considered as an alternative for children for whom other malaria chemoprophylactic regimens would either be ineffective or contraindicated.

Pregnant women. Primaquine may cause hemolysis and hydrops fetalis in fetuses, and because the G6PD status of the fetus is rarely known with certainty, administration of primaquine is contraindicated during pregnancy irrespective of the mother's G6PD status.[167,168] Pregnant women who need primaquine for radical cure of *P. vivax* or *P. ovale* malaria should be treated after they have delivered and may be maintained on weekly chloroquine until delivery.

No data are available on primaquine use in breastfeeding women[169] or excretion of primaquine in breast milk. As a precaution, breast-feeding infants should be tested for G6PD deficiency before primaquine is given to the mother.[5]

COST

For a 14-day trip to a malarious area, including doses taken before, during, and after malaria exposure, the estimated drug costs for prophylaxis are shown in Table 4.[170] These costs do not include testing for G6PD deficiency for primaquine, nor do they include using primaquine for PART when chloroquine, doxycycline, mefloquine, or atovaquone/proguanil are given. The estimated cost for G6PD testing is $25.00.[170]

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