Malaria

Medical Summary

What's New

Tafenoquine has been commercially available in Australia since March 2019 and will be available in the U.S. no earlier than August 2019. Pricing details and coverage by third-party payers is unknown at this time. Destinations and Maps content have been updated to include tafenoquine as a first-line chemoprophylaxis option to allow users time to become familiar with the properties of and indications for this first new drug for chemoprophylaxis in almost 20 years.

Shoreland's Recommendations for Chemoprophylaxis of Malaria

The choice of antimalarial drug for most malarious areas depends on traveler-related factors, such as trip duration, medical history, age, potential and previous drug intolerance, likely ability to adhere to the multistep tafenoquine (TQ) regimen, G6PD testing logistics (for TQ), economic factors (atovaquone-proguanil can be costly for lengthy trips), and whether mefloquine resistance exists at the destination. The summary below may require additional explanation, which is found in the full text of this article.

- In areas with malaria, atovaquone-proguanil, doxycycline, mefloquine, and TQ are considered equally as first-line drug options (do not use mefloquine in areas of Southeast Asia where drug resistance occurs).
- In practice, for short-stay travel (< 2-3 weeks), daily atovaquone-proguanil may be preferable to doxycycline or mefloquine because the drug can be discontinued 7 days after departure from a malarious area; it may also be preferable to TQ because of concise dosing instructions and because G6PD testing is not needed. Longer courses of atovaquone-proguanil appear to be safe.
- TQ prevents initial parasite development in the liver, acts on the blood-stage parasites of all malaria species including *P. falciparum*, and is also active against the dormant hypnozoites of *P. vivax* and *P. ovale* (which cause late relapses after return home), making the drug unique among chemoprophylactic agents and, in terms of mechanism of action, a superior agent. TQ was shown to be well-tolerated and efficacious in licensing trials; however, as a newly approved drug, more extensive efficacy and safety databases are still forthcoming.
- TQ, with weekly dosing, will be most easily integrated into highly structured environments (e.g., multinational corporations, nongovernmental organizations, military, and diplomatic services) with substantial cohorts of regular travelers who can be tested once for G6PD.
- Mefloquine, if tolerated, is preferable for long-stay travel (> 6 months) due to the current 6-month limit on TQ use.
- Chloroquine is an additional first-line drug used in a very few geographic areas of the world.
- Mefloquine and chloroquine are considered safe in pregnancy.
- Mefloquine packaging carries warnings in most countries stating that neuropsychiatric and vestibular adverse reactions can persist long-term or permanently, even after discontinuation of mefloquine.
- TQ and doxycycline have limitations on pediatric use; prescribing one of the other drugs for the entire family is often desirable.

Shoreland Recommendations for Standby Emergency Treatment

Shoreland recommends either *atovaquone-proguanil* or an *artemisinin-based combination therapy (ACT) drug* (such as coartemether or dihydroartemisinin-piperaquine) as the drug of choice for standby emergency treatment (SBET), should this strategy be chosen by the traveler; however, resistance to artemisinin is reported along the borders in Southeast Asia, especially Burma, Cambodia, Thailand, and Vietnam. Currently, ACT may still be used effectively in areas of possible resistance to artemisinin. Even local patients with a proven delayed clearance phenotype may still be treated successfully with standard ACT regimens. See Standby Emergency Treatment for additional information.

- Atovaquone-proguanil is available in the U.S. as the brand Malarone (GSK) and in generic forms (Glenmark Generics and Mylan Pharmaceuticals).
- Coartemether is available as Coartem in the U.S. and as Riamet in Europe.
- Dihydroartemisinin-piperaquine is available as Eurartesim in Europe and as Artekin or Duo-Cotecxin in some other

countries.

- Coartem and Eurartesim are not approved or indicated for the treatment of severe malaria or for malaria chemoprophylaxis.

Introduction

Malaria is caused by a protozoan parasite that lives within red blood cells (RBCs) and is primarily transmitted by the bite of *Anopheles* mosquitoes, generally between dusk and dawn. Malaria remains the most frequent infectious cause of death for travelers going to tropical and subtropical countries, but infection can usually be prevented using antimalarial medications and personal protective measures against mosquito bites.

Epidemiology

Malaria occurs in approximately 100 countries that are visited by more than 125 million travelers yearly, including countries in Africa, Central and South America, South Asia, Southeast Asia, the Middle East, and islands of the South Pacific. In 2015, an estimated 214 million cases of malaria and 438,000 deaths were reported worldwide. Most cases and deaths occur in sub-Saharan Africa.

In the U.S., 1,727 cases of malaria were reported (2 congenital cases and 10 deaths) in 2013, representing a 2% increase from the 1,687 cases (6 deaths) reported in 2012. Among the reported cases, *P. falciparum* (61%), *P. vivax* (14%), *P. ovale* (4%), and *P. malariae* (3%) were identified. Of the 1,727 cases, 1,720 were imported, of which 1,517 had information on the region where malaria was acquired: Africa (82%), especially from West African countries; Asia (11%); Central America and the Caribbean (3%); South America (3%); Oceania (1%); and Europe (< 1%). Of the 961 cases reported in U.S. civilians, 42 (4%) had adequate chemoprophylaxis as recommended by CDC.

Mode of Transmission

Malaria is caused by a protozoan parasite that lives within RBCs and is transmitted by the bite of *Anopheles* mosquitoes found in almost all tropical and subtropical countries. Transmission usually occurs between dusk and dawn because the *Anopheles* mosquitoes generally feed only at night. Occasionally, malaria is transmitted through blood transfusion, congenitally, or through contaminated needles and syringes.

Five *Plasmodium* species are known to cause malaria in humans: *P. falciparum* (the most serious, potentially lethal form), *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*. Of these strains, *P. falciparum* and *P. vivax* pose the greatest threat to travelers.

- *P. falciparum* is the most prevalent malaria parasite on the African continent and is responsible for the most malaria-related deaths globally.
- *P. vivax* has a wider distribution than *P. falciparum* and predominates in many tropical and subtropical countries outside Africa.
- *P. knowlesi* (a monkey malaria) has been reported in travelers going to rainforests and/or their fringe areas in Southeast Asia, within the range of the natural monkey hosts and mosquito vectors of this infection. These areas include parts of Cambodia, China, Indonesia, Laos, Thailand, Burma (Myanmar), Malaysia, the Philippines, Singapore, and Vietnam. Like *P. falciparum*, *P. knowlesi* can cause a severe and fatal infection. The currently licensed chemoprophylactic agents are expected to confer protection against this organism. Travelers going to these areas should also use insect precautions.

Risk Factors

The estimated risk of acquiring malaria varies markedly, even within the same country. The risk depends on the intensity of transmission, traveler's itinerary, location within a country (e.g., urban vs. rural), type of accommodation, anticipated activities where the traveler will spend the evening and nighttime hours, season, duration, and type of travel. For example, short-stay travelers living in urban centers and staying in air-conditioned hotels will be at a much lower risk than long-stay, adventurous travelers living in rural areas. Generally, malaria is transmitted in urban and rural areas in sub-Saharan Africa and South Asia. Most of the world's malaria occurs in sub-Saharan Africa, and risk to the traveler is considerably higher there than anywhere else. In most other parts of the world, malaria transmission occurs only in rural areas. Malaria transmission does not occur above 2,500 m (8,200 ft), but the maximum transmission altitude varies greatly by country. See individual country malaria maps for details.

The estimated relative risks of malaria for persons who are not taking drugs to prevent malaria are as follows:

Table 1: Estimated Relative Risks of Malaria	
Region*	**Level of Risk**
Sub-Saharan Africa	High
Pacific Islands: Papua New Guinea, Solomon Islands, Vanuatu	High
South Asia	Intermediate
Hispaniola	Intermediate
Southeast and East Asia	Low
Central and South America	Low
*Relative risk varies within each region.	

Transmission in other areas of the world is generally much less intense, and most of the higher-risk regions within these areas are outside the typical resort destinations or travel itineraries.

Persons who plan to donate blood after a trip to a malarious area should be advised to check with their blood center about donor deferral criteria. Overall, the U.S. Red Cross guidelines recommend deferral for 3 years for individuals who have lived in a malarious area or who have been treated for documented malaria. Visitors to malarious areas are generally deferred for 1 year after last exposure.

Clinical Presentation

Malaria is characterized by fever and influenza-like symptoms (chills, sweats, myalgia, and headache) that may be episodic but very often have an irregular pattern in travelers. Vomiting, diarrhea, abdominal cramping, and cough also may occur, and the disease may be associated with anemia, thrombocytopenia, and jaundice.

Malaria caused by *P. falciparum* usually occurs about 10 to 12 days after infection, is potentially life threatening, and is considered a medical emergency. Without prompt treatment, parasites in RBCs can sequester in end-organ capillaries leading to cerebral malaria, renal failure, pulmonary edema, shock, and death.

Symptoms caused by the nonfalciparum malaria species may appear from 14 days to many months after infection. *P. vivax* and *P. knowlesi* infections can sometimes lead to end-organ damage and fatality.

Travelers should be educated about malaria symptoms and informed that:

- No malaria chemoprophylactic regimen is 100% effective.
- Symptoms may be mild and may mimic influenza, gastroenteritis, or other common infections; malaria should be suspected for any fever that develops during or after travel to a risk area.
- Early treatment is usually effective, and delay of appropriate therapy can have serious or even fatal consequences; if symptoms of malaria occur, prompt medical attention must be sought.
- The physician should be informed of the recent travel history, and blood films should be requested; in the event of a negative film, 2 additional tests should be carried out 12 to 24 hours apart.

Diagnostic Test

In the U.S., a rapid diagnostic test (RDT), the BinaxNOW Malaria card test, is available and licensed for laboratory diagnosis of malaria but not for clinician (in office or emergency room) or patient use. This FDA-approved test provides qualitative results (using a single drop of blood) within 5 to 15 minutes without microscopy. The test differentiates falciparum from nonfalciparum malaria but does not allow for speciation of nonfalciparum infections. The test is comparable to microscopy (95% sensitive) for moderate-to-high *P. falciparum* parasitemias but is significantly less sensitive for low-level infection. Sensitivity for *P. vivax* infection is approximately 85%.

The RDT is highly specific (approximately 99%). A positive test mandates immediate malaria treatment. However, positive results should be followed by microscopy and polymerase chain reaction (PCR) whenever possible to accurately identify the species. In cases of nonfalciparum malaria, microscopy is needed to determine the species of malaria parasite. Because the RDT is qualitative and not quantitative, it cannot be used to determine initial parasite density or the parasitological response to therapy. Therefore, serial microscopy is needed to quantify the proportion of infected RBCs, an important prognostic indicator that can be used to monitor response to therapy. All negative results should also be followed by microscopy to confirm results.

Many hospital laboratories lack expertise in malaria microscopy, and the RDT will immediately and accurately detect almost all moderate-to-high parasitemias of potentially life-threatening *P. falciparum* infection.

Relapsing Malaria

Two species of plasmodia, *P. vivax* and *P. ovale*, can cause clinical relapse of disease even with adequate chemoprophylaxis. Relapse can occur weeks or months (and rarely, up to 2 years) after the initial infection with *P. vivax* or *P. ovale*, whether initially symptomatic or not. These 2 species form dormant stages in the liver, called hypnozoites, which are not affected by traditional chemoprophylactic drugs, including atovaquone-proguanil, chloroquine, doxycycline, or mefloquine.

A relapse can occur even if the person harboring hypnozoites of *P. vivax* or *P. ovale* had no symptoms of malaria during or after initial infection because parasites in the bloodstream would have been completely suppressed by the chemoprophylactic drug. Many people do not know that they were infected with *P. vivax* or *P. ovale* until a relapse occurs, long after initial exposure.

Frequency of relapse and the prepatent or latent period before relapse of *P. vivax* malaria vary between geographic zones. The zone comprising Southeast Asia, Papua New Guinea, and Melanesia has the highest predicted incidence of relapse (800-1,200 per 100,000 person days) and the fastest mean time to relapse (approximately 45 days). The zone comprising Northern Asia and Europe has the lowest incidence of relapse (130 per 100,000 person days) and the longest mean time to relapse (approximately 10 months), but relapse may occur several years after exposure. Travelers should be made aware of the likelihood and timing of relapse episodes of *P. vivax* malaria after their return from an endemic area. See *Literature Watch Review:* Relapse in *Plasmodium vivax* Malaria.

Tafenoquine (TQ) and primaquine (PQ) are the only available drugs that act on hypnozoites and may be given as presumptive antirelapse therapy (PART); see Tafenoquine and Primaquine in the chemoprophylaxis section below.

Prevention

No vaccine is available or imminent for the prevention of malaria in travelers. Prevention in travelers typically involves a combination of personal protective measures, chemoprophylaxis, and prompt medical evaluation of fever or influenza-like illness, or SBET where medical evaluation is unavailable.

Personal Protective Measures

Personal protective measures can reduce the risk of malaria, but appropriate chemoprophylaxis should be considered. Mosquitoes that transmit malaria (*Anopheles* spp.) are generally night biters with activity between dusk and dawn. Travelers should:

- Wear clothing that covers as much skin as practicable.
- Apply a repellent to all exposed, nonsensitive areas of the body during biting activity time. When both repellent and sunscreen are used, apply the sunscreen first, using a product with an SPF of 30 to 50. Limited data suggest some reduction of repellency when sunscreen is applied over the repellent.
- Use a repellent containing DEET (N,N-diethyl-meta-toluamide; 30%–35% concentration) or, alternatively, a repellent containing picaridin (20% concentration or greater for tropical destinations; also known as icaridin). Picaridin, unlike DEET, has a pleasant smell and does not dissolve plastic materials.
- Treat outer clothing, boots, tents, and sleeping bag liners with permethrin (or other pyrethroid) when traveling in an area of very high risk for mosquito-borne or tick-borne diseases.
- Sleep under a permethrin-impregnated bed net when at high risk of malaria if not sleeping in a sealed, air-conditioned room. Regularly check the net for rips and tears and keep it tucked in around the bed at all times. Ensure that all open windows have insect screens.
- Use spatial repellent products in the form of an aerosol spray, vaporizer device, or smoldering coil. These products usually

contain a pyrethroid (e.g., metofluthrin or allethrin).

See *Insect Precautions*.

Prevention with Chemoprophylaxis

The following table summarizes the doses and schedules for antimalarial medications.

Table 2: Drugs Used in Malaria Prevention[1]

Drugs[2]	Tablet Size	Adult Dose and Schedule	Pediatric Dose and Schedule[3]	Comments
Drugs of Choice				
Atovaquone-proguanil (Malarone and generics; Malanil in South Africa)	Adult: 250/100 mg Pediatric: 62.5/25 mg[4] (Pediatric tablets are licensed in both Canada and the U.S.)	**Dose**: 1 tablet *Before entering malarious area*: 1-2 days prior *While in malarious area*: Once daily *After leaving malarious area:* Once daily for 7 days	**Dose**: 5-8 kg: ½ pediatric tablet[5] 9-10 kg: ¾ pediatric tablet[5] 11-20 kg: 1 pediatric tablet (¼ adult tab) 21-30 kg: 2 pediatric tablets (½ adult tab) 31-40 kg: 3 pediatric tablets (¾ adult tab) > 40 kg: adult dose (1 adult tablet) **Schedule**: Same as adult	Drug of choice for malaria chemoprophylaxis in most short-stay travel situations
Chloroquine phosphate (Generic only in the U.S.)	500 mg (300 mg base) (500 mg tablets not available in Canada) 250 mg (150 mg base); only generics are available in 250 mg tablet size. Syrup formulation is available in some countries, but quality may be an issue.	**Dose**: 500 mg *Before entering malarious area*: 1-2 wks prior *While in malarious area*: Once weekly *After leaving malarious area:* Once weekly for 4 wks	**Dose**: 8.3 mg/kg (5 mg/kg base) orally Maximum dose: 500 mg (300 mg base) **Schedule**: Same as adult	Alternative first-line drug in limited areas of the world where chloroquine resistance has not been reported
Doxycycline hyclate (Vibramycin, VibraTabs, and other brand names and generics)	20 mg; 50 mg; 100 mg (only 100 mg available in Canada)	**Dose**: 100 mg *Before entering malarious area:* 1-2 days prior *While in malarious area:* Once daily *After leaving malarious area:* Once daily for 4 wks	**Dose**: 2.2 mg/kg, orally[6] Maximum dose: 100 mg **Schedule**: Same as adult	Alternative first-line drug in all areas Contraindicated in children aged < 8 yrs in the U.S. Contraindicated in children aged < 12 yrs in the U.K.
Doxycycline monohydrate (Monodox, Adoxa, and generics)	Not available in Canada	**Dose**: 100 mg *Before entering malarious area:* 1-2 days prior *While in malarious area:* Once daily *After leaving malarious area:* Once daily for 4 wks	**Dose**: 2.2 mg/kg, orally[6] Maximum dose: 100 mg **Schedule**: Same as adult	Alternative first-line drug in all areas May be better tolerated than hyclate salt Contraindicated in children aged < 8 yrs in the U.S. Contraindicated in children aged < 12 yrs in the U.K.
Mefloquine	250 mg[7] (228 mg	**Dose**: 250 mg	**Dose per CDC**:	Alternative first-line drug in all

hydrochloride (Lariam in other countries and generic only in the U.S.)	base)	*Before entering malarious area:* ≥ 2 wks prior (or 3 to 4 wks if a concern exists about adverse effects) *While in malarious area:* Once weekly *After leaving malarious area:* Once weekly for 4 wks	≤ 9 kg: 5 mg/kg (4.6 mg/kg base) 10-19 kg: ¼ tab 20-30 kg: ½ tab 31-45 kg: ¾ tab > 45 kg: 1 tab **Dose per WHO**: 5 mg/kg **Schedule**: Same as adult	areas outside of Southeast Asia If tolerated, preferable for long-stay travel (> 6 months)
Tafenoquine (TQ; Arakoda [Kodatef in Australia], Krintafel [Kozenis in Australia])	Arakoda: 100 mg (Available only as prepackaged boxes of 16 tablets in the U.S. and in boxes of 8 or 16 tablets in Australia)	For primary chemoprophylaxis (use limited to 6 mos duration) **Dose**: 200 mg (2 tablets) *Before entering malarious area:* Once daily for 3 consecutive days *While in malarious area:* Once weekly starting 7 days after the previous dose *After leaving malarious area:* 1 dose, 7 days after the previous dose	Arakoda: Not approved for persons aged < 18 yrs	G6PD testing is mandatory before use. Alternative first-line drug in all areas Weekly dosing (after 3-day loading regimen; Friday-Saturday-Sunday may be most convenient) and good tolerability make it preferable in many travel scenarios. Pregnancy testing is recommended. TQ tablets should not be crushed or chewed but swallowed whole with food; dose should be repeated (once only) if vomiting occurs within 1 hr of administration. Travelers should receive explicit instructions on missed doses (see Table 4: Tafenoquine Missed Dose Replacement).
	Arakoda: 100 mg Krintafel: 150 mg	For PART (from *P. vivax* and *P. ovale*) **Dose/schedule**: 300 mg once (2 or 3 tablets depending on brand)	Arakoda: Not approved for persons aged < 18 yrs Krintafel: Not approved for persons aged < 16 yrs	G6PD testing is mandatory before use. Pregnancy testing is recommended.
Alternative Drug				
Primaquine phosphate (PQ; generic only in the U.S.)	26.3 mg (15 mg base)	For primary chemoprophylaxis **Dose**: 52.6 mg (30 mg base) *Before entering malarious area:* Once daily, 1-2 days prior *While in malarious area:* Once daily *After leaving malarious area:* Once daily for 7 days.	For primary chemoprophylaxis **Dose**: 0.8 mg/kg (0.5 mg/kg base) orally Maximum dose: 52.6 mg (30 mg base) **Schedule**: Same as adult	G6PD testing is mandatory before use. Prophylactic use only in areas with predominantly *P. vivax*
	26.3 mg (15 mg base)	For PART (from *P. vivax* and *P. ovale*) **Dose/schedule**: 52.6 mg (30 mg base) once daily for 14 days	For PART (from *P. vivax* and *P. ovale*) **Dose/schedule**: 0.8 mg/kg (0.5 mg/kg base) orally once daily for 14 days Maximum dose: 52.6 mg (30 mg base)	G6PD testing is mandatory before use. Can be used for PART after leaving a malarious area in persons who have not taken TQ or PQ for primary chemoprophylaxis

1. Check package insert for recommendations regarding taking with water and/or food.
2. Use of trade names is for identification and does not imply endorsement. Drugs are listed alphabetically.
3. 1 kg = 2.2 lb.
4. Pediatric tablet (available in the U.S.) strength = 1/4 adult tab.
5. Off-label use (recommended by Shoreland and CDC). Shoreland's recommendation for chemoprophylactic dosage in this weight range is based on extrapolation from FDA-labeled treatment dosing for the same weight range.
6. Doxycycline is available as a room-temperature–stable liquid formulation, which is suitable for children.
7. In some countries (e.g., some countries in Europe), 250 mg Lariam tablets contain 250 mg of mefloquine base, which is 274 mg of mefloquine hydrochloride.

Indications

The travel itinerary should be reviewed in detail and compared with Travax Destinations regarding risk areas within a given country to determine the extent that the traveler will be at risk for malaria. Because *Anopheles* mosquitoes bite from dusk to dawn, antimalarial drugs are only recommended for travelers who will have exposure during those hours in malaria risk areas. Additional factors should be considered, such as whether the traveler has previously experienced an adverse reaction or allergy to the antimalarial drug of choice and whether medical care will be readily accessible during travel.

Adults who grew up in malarious areas generally believe themselves to be immune for life against malaria and would not consider the need for chemoprophylaxis when they return "home" to visit friends and relatives. Immunity to malaria wanes within 6 months from last exposure to malaria and chemoprophylaxis is indicated in these individuals, similar to first-time travelers going to the region.

Chemoprophylactic Regimens for Adults

See Table 2: Drugs Used in Malaria Prevention. See also Chemoprophylaxis during Pregnancy and Chemoprophylaxis while Breastfeeding.

General

Using chemoprophylaxis in addition to personal protective measures against mosquito bites is an important safeguard for travelers going to malarious areas. Travelers should be reminded that the risk of side effects exist regardless of chemoprophylaxis choice. However, the risk of side effects must be weighed against the risk of a potentially fatal infection with *P. falciparum*.

No global consensus exists (even among physicians within the same country) as to the optimal chemoprophylaxis regimen. Other travelers en route may have been prescribed an assortment of regimens with varying effectiveness, including drugs unavailable in the U.S. Travelers should be instructed to adhere to their own regimen. If intolerable side effects arise, they should contact the original prescribing health provider (if possible) for advice.

Chloroquine, doxycycline, and mefloquine act only on the blood-stage parasites. These drugs do not penetrate the liver to act on parasites during the initial incubation phase of development. These antimalarials must be continued for 4 weeks after the end of exposure to eradicate any parasites that may still be released from the liver. Atovaquone-proguanil prevents initial parasite development in the liver (as well as acting on the blood-stage parasites) and can be discontinued 1 week after the end of exposure. TQ prevents initial parasite development in the liver, acts on the blood-stage parasites, and is active against the dormant hypnozoites of *P. vivax* and *P. ovale*. The use of 3 different modes of action make TQ unique among chemoprophylactic agents. Atovaquone-proguanil, doxycycline, mefloquine, or TQ are considered equally as first-line drugs (unless mefloquine resistance also occurs).

Antimalarial regimens require daily or weekly dosing (details in Table 2: Drugs Used in Malaria Prevention). TQ also requires a 3-day loading regimen. Travelers often find Sunday to be the most convenient and easy-to-remember day for any of the weekly dosing regimens. Chemoprophylaxis should be started 1 day before travel to malarious areas when taking atovaquone-proguanil, doxycycline, or PQ (a second-line agent) and 1 week before travel when taking chloroquine. For TQ, travelers may consider taking the loading doses on the Friday, Saturday, and Sunday before entering the malarious area and then take the maintenance doses every Sunday once in the malarious areas. For mefloquine, travelers should start medication 2 to 3 weeks prior to travel. This is necessary to accumulate adequate blood levels of mefloquine, allow evaluation and treatment of any potential side effects, and if needed, to have an alternative drug prescribed by the traveler’s health care provider to be

purchased prior to departure. In determining malaria regimens, be aware that the first day in a malarious area may not correspond to the first day in the destination country because many itineraries may begin in an urban or nonmalarious area of a country or in a country that is only partly malarious.

Malaria chemoprophylaxis should be continued for as long as exposure occurs and for 1 to 4 weeks after exposures (depends on the drug; Table 2: Drugs Used in Malaria Prevention). Except for chloroquine, no definitive data exist on the absolute safety of very long-term use of antimalarial drugs. TQ is limited to 6 months of use (see Long-Term Chemoprophylaxis). Conversely, even a short exposure of 1 to 2 days in an area with sustained transmission is enough to warrant a full course of chemoprophylaxis.

Atovaquone-Proguanil

Atovaquone-proguanil (Malarone [GSK] or generic) is a fixed combination of atovaquone (250 mg) and proguanil (100 mg) in 1 tablet (adult dose; for dosing see Table 2: Drugs Used in Malaria Prevention). This formulation is available in the U.S. and in almost all developed countries and is by far the most widely prescribed malaria chemoprophylactic drug. Atovaquone-proguanil is effective against chloroquine- or mefloquine-resistant *P. falciparum* malaria (Southeast Asia). A pediatric formulation containing one-fourth of the adult dose is also available.

- The drug has equal efficacy to doxycycline and mefloquine and appears to be very safe (but expensive) for the long-stay traveler. Comparative studies with TQ are not available.
- Atovaquone-proguanil has become the drug of choice for many practitioners and travelers for the prevention of malaria among short-stay travelers and for self-treatment of malaria. Atovaquone-proguanil is equally effective in destinations where chloroquine is the drug of choice and can be used for short-stay travel of less than 2 weeks in these countries due to the convenience of the dosing regimen. Note: If atovaquone-proguanil is being used for chemoprophylaxis, it should not be used for SBET in the same traveler. See Standby Emergency Treatment.
- Because atovaquone-proguanil is incompletely absorbed on an empty stomach, it should be taken with a meal or a fatty drink (such as milk) and at the same time each day to maintain therapeutic blood levels.
- Preliminary data from 2 small studies, indicating the efficacy against *P. falciparum* in regimens where atovaquone-proguanil is discontinued on the last exposure day, are insufficient to support a change in established regimens (see *Literature Watch Review:* Effectiveness of Short Prophylactic Course of Atovaquone-Proguanil). However, the findings may be reassuring to those who, for a variety of reasons, discontinued atovaquone-proguanil several days early.
- Generic atovaquone-proguanil is available in the U.S. as an alternative to Malarone and is available in both adult (250 mg/100 mg) and pediatric (62.5 mg/25 mg) formulations. Generic formulations are available from Glenmark Generics (adult tablets made in India; pediatric tablets made in Canada by GSK and packaged in the U.S.) and Mylan Pharmaceuticals (adult and pediatric tablets made in India).

Contraindications

Atovaquone-proguanil is contraindicated for:

- Pregnant women, due to lack of available safety data for the atovaquone component
  - Three small published studies suggest that atovaquone-proguanil use in pregnancy is safe and without significant toxicity to the fetus; however, further data are needed.
- Persons with severe renal failure (creatinine clearance < 30 mL/min)
- Persons with allergy to either atovaquone or proguanil

Precautions

Concomitant administration of tetracycline, metoclopramide, rifampin, or rifabutin decreases the concentration levels of atovaquone-proguanil.

No data exist on the use of atovaquone-proguanil for long-term (> 2 months) chemoprophylaxis in persons with moderate renal failure (creatinine clearance 30-50 mL/min).

Adverse Effects

Given that side effects from atovaquone-proguanil were no different from the placebo in several chemoprophylaxis studies, it appears to be very safe. Separate individual doses greater than 100 times the chemoprophylactic dose of atovaquone and proguanil have been tolerated without apparent toxicity.

- When the drug is used for treatment, side effects such as nausea, vomiting, diarrhea, and abdominal pain occur occasionally; seizures and rash are rare.
- Post marketing adverse reactions include skin/hypersensitivity reactions (i.e., rash, photosensitivity, angioedema, urticaria, rare cases of anaphylaxis, erythema multiforme, and Stevens-Johnson syndrome), hepatitis, and central nervous system reactions (i.e., rare cases of seizures and psychotic events).

Chloroquine

Chloroquine chemoprophylaxis (only generic chloroquine is currently available in the U.S.) is currently indicated for chemoprophylaxis in very few countries due to resistance (for dosing see Table 2: Drugs Used in Malaria Prevention). Note: The U.S. package insert for chloroquine continues to specify 8 weeks of postexposure dosing in contrast to the standard 4 weeks, which has been recommended by all authoritative sources, including CDC and WHO for many decades.

For imminent departures, a loading dose of chloroquine can be achieved by taking a standard dose (300 mg base), repeating it 6 hours later, and then taking a standard dose weekly after that.

Hydroxychloroquine (Plaquenil and generics), although not a primary antimalarial, may be used for chemoprophylaxis in chloroquine-sensitive areas if chloroquine is unavailable or in a situation where the traveler is already taking hydroxychloroquine daily for another indication (e.g., treatment of rheumatic diseases). If the traveler is not taking hydroxychloroquine, the dose is 400 mg weekly taken on the same schedule as chloroquine. In a situation where a traveler is already taking hydroxychloroquine for a medical condition (e.g., lupus, rheumatoid arthritis), a daily dose of at least 100 mg is adequate to provide the same level of protection as that of the 400 mg weekly dose recommended for malaria chemoprophylaxis.

Contraindications

Chloroquine is contraindicated in persons with:

- Allergy to chloroquine or related compounds
- Retinal or visual field changes
- Epilepsy or chronic seizure disorder

Precautions

Precautions include:

- Chloroquine should be used with caution in persons with a history of G6PD deficiency, preexisting auditory damage, hepatic disease, or alcoholism.
- Complete blood cell counts should be done periodically if patients are on prolonged therapy.
- Irreversible retinal damage has been observed in some patients on high-dose therapy with chloroquine. For long-term chloroquine therapy, consider periodic ophthalmologic examinations if the cumulative dose of chloroquine might exceed 100 g. See also Drug Compatibility.
- All patients on long-term therapy should be examined periodically to detect muscle weakness; if weakness occurs, discontinue chloroquine.
- Chloroquine may exacerbate porphyria and may precipitate a severe attack of psoriasis.
- Chloroquine has an extremely narrow therapeutic ratio, and as few as 2 tablets can be fatal to a young child. Travelers should be strongly warned to keep this drug out of the reach of children.

Adverse Effects

Chloroquine rarely causes serious adverse reactions when taken at chemoprophylactic doses for malaria. Those who experience uncomfortable side effects may tolerate the drug better by taking it with meals or in divided, twice-weekly doses.

- Minor side effects may occur, such as gastrointestinal disturbance, headache, dizziness, blurred vision, and pruritus (especially in dark-skinned people).
- Other possible adverse events include retinal damage (see Precautions), auditory changes, muscle weakness, or atrophy. Rarely, hematological (e.g., aplastic anemia) or cardiac changes (e.g., hypotension or ECG changes) may occur.
- Severe neuropsychiatric disturbances (e.g., seizures, psychosis, encephalopathy) have been reported at rates similar to mefloquine (approximately 1 in 13,000 travelers).

Doxycycline

Doxycycline is a recommended drug of choice despite some minor disadvantages in protecting against *P. vivax* in tropical zones (for dosing see Table 2: Drugs Used in Malaria Prevention). The short half-life of doxycycline results in inadequate chemoprophylactic blood levels immediately after cessation of the 4-week posttravel course, so that early relapses will not be suppressed as would be the case with longer acting drugs. (See discussion of relapsing malaria.).

Although the licensed duration of use for doxycycline in the U.S. is 4 months, data indicate that it can be used safely for up to 2 years.

Insufficient data exist regarding the antimalarial chemoprophylactic efficacy of related medications such as minocycline; therefore, these drugs should not be used for antimalarial chemoprophylaxis. Persons on long-term minocycline should be switched to doxycycline 1 to 2 days prior to travel and only restarted on minocycline once the full course of doxycycline is completed.

Contraindications

Doxycycline is contraindicated for:

- Persons with an allergy to doxycycline or tetracycline

Precautions

Doxycycline should be used with caution in:

- Pregnant women, especially after 15 weeks' gestation when fetal tooth and bone development begin
- Children aged < 8 years (aged < 12 years in the U.K.). Doxycycline may be used in young children for up to 21 days, but this limit precludes use for malaria chemoprophylaxis.

Adverse Effects

Doxycycline-induced photosensitivity, usually manifested as an exaggerated sunburn reaction, is clearly more common with exposure to the tropical sun. Risk can be minimized by avoiding prolonged, direct sun exposure, using sunscreen that absorbs both UVA and UVB radiation, and wearing a hat. Doxycycline should be discontinued at the first sign of any erythema.

- Doxycycline use is associated with an increased frequency of Candida vaginitis, which should be discussed with female patients before prescribing the drug. An antifungal agent, such as fluconazole (150 mg single-dose tablets), should be carried for self-treatment by women who have been prescribed doxycycline.
- Doxycycline is a gastric and esophageal irritant. Gastrointestinal side effects, including esophageal ulceration and gastritis, may be minimized by taking the drug with a meal, in an upright position, and with a full glass of water. The traveler should not lie down for at least 30 minutes after ingestion. See also Drug Compatibility.

Mefloquine

Mefloquine (available only as a generic in the U.S.; for dosing, see Table 2: Drugs Used in Malaria Prevention) is the most poorly tolerated of the first-line malaria chemoprophylactic agents but weekly dosing make it convenient for very long-term use and in young children on shorter trips because TQ is not approved for pediatric use.

Starting mefloquine 2 to 3 weeks prior to travel allows for the accumulation of adequate blood levels of mefloquine and for any potential side effects to be evaluated and treated and an alternative drug started if necessary. Adverse events of mefloquine can also be predicted by using a loading dose (off-label use) of 1 tablet daily for 3 days and then weekly thereafter. The adverse events of mefloquine will occur within the first week of a loading dose compared with the third to seventh week with weekly dosing. Due to the long half-life of mefloquine (3 weeks), adverse effects after a loading dose will persist for as long as with weekly dosing. See Adverse Effects, below.

Contraindications

Mefloquine is contraindicated for persons who have:

- Allergy to mefloquine or related compounds (e.g., quinine) or any excipients contained in the formulation
- Active or recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, or other major psychiatric disorder
    - In Europe, mefloquine is also contraindicated in persons with a history of depression.

- History of convulsions, including epilepsy
- Treatment with halofantrine or ketoconazole
  - Due to the risk of potentially fatal prolongation of the QTc interval, neither drug should be given simultaneously with or within 15 weeks of the last dose of mefloquine.
- Cardiac conduction abnormalities

Precautions

Precautions include:

- Use mefloquine with caution in patients with a history of depression, cardiac disease (see Adverse Effects, below), and epilepsy.
- Occurrence of psychiatric symptoms (such as unexplained acute anxiety, depression, restlessness, or confusion) during chemoprophylactic use may be prodromal to a more serious event so the drug should be discontinued and an alternative medication substituted.
- Neuropsychiatric symptoms can be difficult to identify in children; therefore, vigilance is required to monitor for their occurrence, especially in nonverbal children. If mefloquine is administered for longer than 1 year, periodic ophthalmologic and liver function examinations and evaluation of neuropsychiatric effects should be performed.
  - Elimination of mefloquine may be prolonged in patients with impaired liver function, leading to higher plasma levels and a higher risk of adverse reactions.
- Mefloquine may increase the risk of convulsions in persons with epilepsy; therefore, it should be prescribed only for curative treatment.
- Caution should be exercised when alertness and fine motor coordination are required (e.g., persons planning to drive, pilot aircraft, or operate machinery).

Refer to package insert for a complete list of precautions and contraindications.

Adverse Effects

The side effects of mefloquine have received widespread media attention for almost 30 years. Mefloquine has been used by more than 20 million people and a large database exists. Approximately 95% of mefloquine users tolerate the drug without discontinuing it.

The FDA-approved mefloquine label includes a *black box warning* stating that neuropsychiatric and vestibular adverse reactions can persist long-term or permanently, even after discontinuation of mefloquine. A similar warning has been incorporated in Europe, which requires the use of mandatory information packets and communication of risks to patients. Individual member states will craft their own recommendations; Switzerland, Germany, Austria, and Italy now restrict the use of mefloquine for chemoprophylaxis to high-risk malaria-endemic areas.

Neuropsychiatric: Reactions range from anxiety, paranoia, and depression to hallucinations and psychotic behavior. Cases of suicidal ideation and suicide have been reported, as well as mood change and panic attack.

Severe neuropsychiatric disturbances (seizures, psychosis, encephalopathy) occur in approximately 1 in 6,000 to 10,000 travelers receiving mefloquine. The risk of disabling neuropsychological problems (e.g., insomnia, nightmares, irritability, depression) occurs on the order of 1:200 to 1:500 users. Up to one-quarter of users will experience vivid dreams, but generally they are not disabling and are well tolerated by travelers.

Neurological: Dizziness or vertigo, tinnitus, and loss of balance have been reported, sometimes continuing for months or years after discontinuation of mefloquine. If neurological symptoms occur, the drug should be discontinued and an alternative medication should be substituted. Mefloquine may increase the risk of convulsion in persons with epilepsy.

Cardiac: Animal studies show that mefloquine, a myocardial depressant, possesses 20% of the antifibrillatory action of quinidine and produces 50% of the increase in the PR interval reported with quinine. Transitory and clinically silent ECG alterations have been reported during the use of mefloquine. Alterations included sinus bradycardia, sinus arrhythmia, first-degree AV-block, prolongation of the QTc interval, and abnormal T waves.

Ophthalmic: Clinically insignificant maculopathy has been noted after long-term (< 1 year) chemoprophylactic use of mefloquine.

Hepatic: Patients with impaired liver function have prolonged elimination of mefloquine, leading to higher plasma levels.

Other: Infrequent reports of chest pain, edema, dyspnea, and pneumonitis of possible allergic etiology exist. Gastrointestinal disturbance and dizziness have occurred with chemoprophylactic doses but tend to be mild and temporary.

Compatibility

Concomitant administration of mefloquine and quinine, quinidine, or other drugs that alter cardiac conduction may produce electrocardiographic abnormalities and increase the risk of seizures.

Tafenoquine and Primaquine

Tafenoquine succinate (TQ; Arakoda [100 mg tablets] and Krintafel [150 mg tablets]) and Primaquine (PQ; available only as generic in the U.S.) are used in 2 different ways to prevent malaria (see Primary prevention as well as Relapse prevention below). TQ (Arakoda), approved for chemoprophylaxis only for persons aged ≥ 18 years, is a new long-acting version of PQ that has been in use for many decades, primarily for relapse prevention.

TQ and PQ are closely related 8-aminoquinoline antimalarials, both of which prevent initial parasite development in the liver (for all malaria species) and are also active against the separate dormant hypnozoites of *P. vivax* and *P. ovale*. TQ (unlike PQ) also acts on the blood-stage parasites of all malaria species, including *P. falciparum*. The use of 3 different modes of action make TQ unique among chemoprophylactic agents and, in terms of mechanism of action, a superior agent.

Because of the potential for life-threatening hemolytic anemia in G6PD-deficient individuals who may not have been tested, travelers should be warned not to share prescribed TQ with others at any time or leave TQ tablets in places where accidental ingestion may occur.

Primary prevention

TQ was approved based on the FDA standard of safety and substantial efficacy; superiority or comparability in efficacy to other licensed drugs was not considered.

Notably, G6PD testing is required, making logistics potentially cumbersome for many one-time, or short-stay travelers. Field efficacy trials, mostly carried out 12 to 20 years ago, are limited to few areas of the world; in 1 limited trial in male soldiers, supportive evidence indicated TQ was comparable to mefloquine in efficacy. After direct human inoculation with blood stage *P. falciparum* parasites, 0 out of 12 TQ-treated subjects developed parasitemia. No clinical trials assessed safety or efficacy for longer than 6 months, so labeled usage is limited to 6 months duration.

PQ requires daily dosing for malaria prevention and has several disadvantages compared to TQ. PQ acts only in the liver (and not in the blood) against *P. falciparum* parasites; if these parasites are not killed during the liver incubation phase due to a missed dose and then enter the bloodstream, the traveler is at risk for falciparum malaria. In field trials, protection rates against *P. falciparum* in Africa were not as high with PQ, as has been found with atovaquone-proguanil, mefloquine, or doxycycline. PQ should not be used for malaria chemoprophylaxis if TQ is available. If TQ is not available, PQ should only be considered when all other options have been definitively eliminated, and then only for short-stay travel to areas in which *P. vivax* constitutes all or nearly all the malaria cases.

Relapse prevention

TQ and PQ can also be given to prevent relapsing malaria after the traveler has left the *P. vivax*/*P. ovale*-endemic area in persons who have not taken TQ or PQ for primary chemoprophylaxis. Presumptive antirelapse therapy (PART) is generally indicated for persons who have had prolonged exposure in malarious areas (> 6 months) where *P. vivax* or *P. ovale* transmission is high and the species constitute a significant proportion of malaria cases or where exposure is intense (e.g., Indonesia, Papua New Guinea, Timor-Leste), regardless of duration. TQ provides single-dose PART and may change the landscape for frequent travelers and long-stay travelers who have not taken TQ for primary chemoprophylaxis. Such persons can be tested a single time for G6PD and then receive single dose TQ for PART after every stay in a malarious area.

Relapses occur because some parasites become dormant in the liver and can be released into the blood stream months or years later when they spontaneously reactivate. TQ and PQ are the only available drugs that act on these dormant forms of *P. vivax* and *P. ovale* in the liver. Travelers with shorter or less intense exposure to *P. vivax* or *P. ovale* (in whom PART is generally not recommended according to current guidelines) need to understand the possibility of a relapse, which may occur months or years later (rare). A relapse can occur even if the traveler did not experience an initial clinical episode of malaria during or right after the actual exposure.

TQ is single-dose PART, which is preferred where available. TQ and PQ are used after the traveler has left a malarious area (starting at the beginning of the last 2 weeks of chemoprophylaxis with chloroquine, doxycycline, or mefloquine, or at the beginning of the last week of chemoprophylaxis with atovaquone-proguanil); PQ should be continued for 1 week after completion of atovaquone-proguanil. For dosing, see Table 2: Drugs Used in Malaria Prevention.

Contraindications

Tafenoquine (TQ) and primaquine (PQ) contraindications include:

- Persons with unknown G6PD status or with known moderate-to-severe G6PD deficiency (< 70% activity on quantitative testing)
- Pregnant women
- Persons with known hypersensitivity reactions to 8-aminoquinolines
- Women who are breastfeeding when the infant is found to be G6PD deficient or if the G6PD status of the infant is unknown (TQ only)
- Persons with a history of psychotic disorders or current psychotic symptoms (TQ only)

Prior to use of TQ/PQ, persons should have quantitative measurement of G6PD activity in their RBCs, and TQ/PQ should only be used in those with ≥ 70% of normal activity. No modified dosing schedule of TQ has been studied for persons with mild deficiency (30%–70% activity). In settings where qualitative (deficient/not-deficient readout) screening (including rapid point of care tests) tests are available, they are highly reliable for males, but females (who may be heterozygotes for G6PD) still require a quantitative test demonstrating ≥ 70% of normal G6PD activity to rule out a potentially serious hemolytic event with TQ/PQ. In most practice scenarios, ≥ 1 day may be needed to get results of either qualitative or quantitative G6PD testing.

G6PD deficiency is most frequently found among persons of African, Asian, Mediterranean, and Middle Eastern descent. Five classes of G6PD deficiency are defined by WHO, with Class I and II being the most severely deficient, Class III is mild to moderate, and Class IV and V as having no clinical significance. This classification system, though widely quoted, is imprecise and cumbersome to apply to TQ/PQ use in practice, and many individuals with Class III deficiency may still have clinically significant hemolysis after TQ/PQ use. Hemolysis in G6PD-deficient individuals may be related to PQ metabolites rather than the drug itself. Thus, administering PQ at less-frequent intervals (e.g., weekly rather than daily) for a longer period (e.g., 8 weeks rather than 2 weeks), provides an efficacious PART regimen while minimizing the risk of hemolysis in persons with Class III or IV G6PD deficiency.

Precautions

Avoid co-administration of TQ with OCT2 and MATE substrates (e.g., dofetilide, metformin).

Adverse Effects

Severe adverse events with TQ and PQ are rare. At present, the cumulative safety database for TQ is limited to approximately 3,000 subjects. In the safety/tolerance studies using the usual therapeutic dosing regimen, very few discontinued due to AEs, and AEs occurred at any time during the regimen. Unusual side effects and safety data for persons aged > 65 years awaits Phase IV postmarketing surveillance.

- Nausea, vomiting, and abdominal pain occur frequently unless the drug is taken with meals. TQ tablets should not be crushed or chewed but swallowed whole with food; a dose should be repeated (once only) if vomiting occurs within 1 hour of administration.
- Hemolysis may occur in persons with G6PD deficiency. Decreased hemoglobin levels (> 3 g/dL) have occasionally been reported after TQ administration in persons with normal G6PD levels on quantitative testing. Monitor all patients for clinical symptoms or signs of hemolysis, including hematuria or jaundice.
- Methemoglobinemia may occur, especially at 30 mg/day of PQ. With TQ, no clinically significant episodes have been observed.
- In pooled data from 4 clinical trials (approximately 350 subjects) conducted in nonmilitary settings, persons in the TQ arm did not have rates of sleep disturbances, depression, or anxiety that differed from the placebo arm.
- Advocacy groups have focused on neuropsychiatric events in several studies conducted in military populations under deployed or combat settings that did not include placebo arms for valid comparisons.
- Psychosis was reported in 3 persons with a history of psychosis or schizophrenia who were given TQ at doses higher than the approved dose.

- Benign corneal deposits (vortex keratopathy), not affecting visual acuity, were seen in 21% of subjects and resolved spontaneously within 12 weeks in 95% of affected subjects and within 48 weeks in 100% of subjects with ≤ 6 months use of TQ during clinical trials.
- Hypersensitivity reactions were reported in clinical trials of TQ.
- Due to the long half-life of TQ, delayed hemolytic anemia, psychosis, methemoglobinemia, or hypersensitivity reactions may occur.
- TQ has not been studied in individuals with renal or hepatic impairment.

Changing Medications during Chemoprophylaxis

Special considerations apply if medications need to be changed midcourse due to side effects (or the desire to take a different medication for the next portion of the trip).

- If a drug that must be taken for 1 week after last exposure (such as atovaquone-proguanil or primaquine) is changed to a drug that must be taken for 4 weeks after exposure (such as doxycycline), then the medication the traveler has switched to must be continued for 4 weeks after the last day of exposure.
- If a drug that must be taken for 4 weeks after last exposure (such as chloroquine, mefloquine, or doxycycline) is changed to a drug that must be taken for only 1 week after exposure (such as atovaquone-proguanil or primaquine), continuation of the second medication for just 1 week after last exposure may be inadequate. Atovaquone-proguanil or primaquine should be continued for 4 weeks after the switch or for 1 week after the last day of exposure, whichever is longer.

Table 3: Changing Medications during the Course of Chemoprophylaxis

Medication to Be Stopped	Medication to Be Started	Comment
Atovaquone-proguanil	Chloroquine	Not recommended
	Doxycycline	Begin doxycycline, continue daily while in malaria-endemic area and for 4 wks after leaving malaria-endemic area.
	Mefloquine	Not recommended
	Primaquine	This switch would be unlikely, but if desired, begin primaquine, continue daily while in malaria-endemic area and for 7 days after leaving malaria-endemic area.
Chloroquine	Atovaquone-proguanil	Take atovaquone-proguanil daily after the switch, continue daily throughout the stay in malaria-endemic area, and: - If the switch occurs ≥ 3 wks before departure from the malarious area, also continue daily for 1 week thereafter. - If the switch occurs < 3 wks before departure from the malarious area, also continue daily for 4 wks after the switch. If the switch occurs after departure from the malarious area, atovaquone-proguanil should be taken daily for 4 wks after the departure.
	Doxycycline	Begin doxycycline, continue daily while in malaria-endemic area and for 4 wks after leaving malaria-endemic area.
	Mefloquine	Not recommended
	Primaquine	This switch would be unlikely, but if desired, begin primaquine, continue daily while in malaria-endemic area and for 7 days after leaving malaria-endemic area.
Mefloquine	Atovaquone-proguanil	Take atovaquone-proguanil daily after the switch, continue daily throughout the stay in malaria-endemic area, and: - If the switch occurs ≥ 3 wks before departure from the malarious area, also continue daily for 1 wk thereafter. - If the switch occurs < 3 wks before departure from the malarious area, also continue daily for 4 wks after the switch. If the switch occurs after departure from the malarious area, atovaquone-proguanil should be taken daily for 4 wks after the departure.

	Chloroquine	Not recommended
	Doxycycline	Begin doxycycline, continue daily while in malaria-endemic area and for 4 wks after leaving malaria-endemic area.
	Primaquine	This switch would be unlikely, but if desired, begin primaquine, continue daily while in malaria-endemic area and for 7 days after leaving malaria-endemic area.
Primaquine	Atovaquone-proguanil	Begin atovaquone-proguanil, continue daily while in malaria-endemic area and for 7 days after leaving malaria-endemic area.
	Chloroquine	Not recommended
	Doxycycline	Begin doxycycline, continue daily while in malaria-endemic area and for 4 wks after leaving malaria-endemic area.
	Mefloquine	Not recommended
Doxycycline	Atovaquone-proguanil	Take atovaquone-proguanil daily after the switch, continue daily throughout the stay in malaria-endemic area, and: - If the switch occurs ≥ 3 wks before departure from the malarious area, also continue daily for 1 wk thereafter. - If the switch occurs < 3 wks before departure from the malarious area, also continue daily for 4 wks after the switch. If the switch occurs after departure from the malarious area, atovaquone-proguanil should be taken daily for 4 wks after departure.
	Chloroquine	Not recommended
	Mefloquine	Not recommended
	Primaquine	This switch would be unlikely, but if desired, begin primaquine, continue daily while in malaria-endemic area and for 7 days after leaving malaria-endemic area.

Missed Doses

Atovaquone-Proguanil

Missed doses of atovaquone-proguanil can be taken later on the same day, with resumption of the normal schedule on the following day. The dose should not be doubled the day after a completely missed dose.

After a missed dose that occurs at a time when exposure to malaria is possible, atovaquone-proguanil must be continued for a minimum of 4 more weeks after resuming chemoprophylaxis and for a minimum of 1 week after the last day of exposure. Atovaquone-proguanil must be continued for a minimum of 4 weeks after the last day of exposure for a missed dose that occurs during the week postexposure.

Chloroquine

A missed dose of chloroquine can be taken a few days later in the week, with resumption of the normal day on the next scheduled dose. A missed dose that is not remembered until the day before the next scheduled dose should not be taken, and the normal schedule should be resumed the next day. The dose should not be doubled the following week if a dose has been completely missed for an entire week.

Doxycycline

Missed doses of doxycycline can be taken later the same day, returning to the previous normal schedule on the next day. The dose should not be doubled the day after a completely missed dose. Due to the short half-life, a completely missed dose of doxycycline may result in complete chemoprophylaxis failure and clinical malaria.

Mefloquine

A missed dose of mefloquine can be taken a few days later in the week, with resumption of the normal day on the next

scheduled dose. A missed dose that is not remembered until the day before the next scheduled dose should not be taken, and the normal schedule should be resumed the next day. The dose should not be doubled the following week when a dose is completely missed for an entire week.

Primaquine

Missed doses of PQ can be taken later on the same day, with resumption of the normal schedule on the following day. The dose should not be doubled the day after a completely missed dose.

Tafenoquine

Table 4: Tafenoquine Missed Dose Replacement

Dose(s) Missed	Replacing Missed Dose(s)
1 loading dose	1 dose of 200 mg (2 of the 100 mg tablets) so that a total of 3 daily loading doses have been taken; begin maintenance dose 1 wk after the last loading dose.
2 loading doses	2 doses of 200 mg (2 of the 100 mg tablets) on 2 consecutive days so that a total of 3 daily loading doses have been taken; begin maintenance dose 1 wk after the last loading dose.
1 maintenance (weekly) dose	1 dose of 200 mg (2 of the 100 mg tablets) on any day up to the time of the next scheduled weekly dose
2 maintenance (weekly) doses	1 dose of 200 mg (2 of the 100 mg tablets) on any day up to the time of the next scheduled weekly dose
3 or more maintenance (weekly) doses	2 doses of 200 mg (2 of the 100 mg tablets), taken as 200 mg (2 of the 100 mg tablets) once daily for 2 days up to the time of the next weekly dose
Terminal chemoprophylaxis dose	1 dose of 200 mg (2 of the 100 mg tablets) as soon as remembered

Examples

Ex 1: A traveler going to Gambia on doxycycline wants to change malaria chemoprophylaxis 6 weeks into her trip due to side effects. She has tolerated atovaquone-proguanil in the past and has access to the drug while traveling. If she makes the switch now, how long should she continue atovaquone-proguanil after leaving the risk area if she is departing Gambia?

- In 2 weeks:
  - **Answer:** Atovaquone-proguanil should be taken daily while she remains in the risk area and daily for 2 weeks after leaving the risk area.
- In 3 weeks:
  - **Answer:** Atovaquone-proguanil should be taken daily while she remains in the risk area and daily for 1 week after leaving the risk area.
- In more than 4 weeks:
  - **Answer:** Atovaquone-proguanil should be taken daily while she remains in the risk area and daily for 1 week after leaving the risk area.

Ex 2: A traveler going to Cambodia on atovaquone-proguanil is having side effects and wants to change to doxycycline. How long should he take the doxycycline?

- **Answer:** Daily while in Cambodia and continue taking daily for 4 weeks after leaving the risk area.

Ex 3: A traveler on a 5-day trip to southern Azerbaijan on primaquine loses his medication with 3 days left in the country. He is able to obtain a supply of doxycycline. How long should he take the doxycycline?

- **Answer:** Daily while in Azerbaijan and continue taking daily for 4 weeks after leaving the risk area.

Ex 4: A traveler has returned home from a 2-week trip to the Amazon regions of Peru and Brazil, during which time he was taking atovaquone-proguanil chemoprophylaxis. However, during the last 5 days of his trip, he developed severe gastroenteritis with vomiting and was unable to take his atovaquone-proguanil for at least 3 days. He restarted atovaquone-proguanil 2 days prior to leaving, and you are seeing him in your office 3 days after his return. How long should he continue

his atovaquone-proguanil chemoprophylaxis?

- **Answer:** Take daily for 4 weeks from the time he left the risk area.

Ex 5: A traveler is spending 3 months in a risk area of Guatemala and then will travel to the Amazon basin for a 2-week river cruise prior to traveling home, but he is concerned about the cost of taking atovaquone-proguanil for his entire trip. He is wondering if he can take chloroquine for his travels in Guatemala and then switch to atovaquone-proguanil for the Amazon cruise, and how best to do this.

- **Answer:** Yes, he can do this, as long as he takes chloroquine on schedule in Guatemala, and changes to atovaquone-proguanil 1 to 2 days before entering the Amazon. Once he has started his atovaquone-proguanil, he no longer needs to take chloroquine. However, he will need to continue his daily atovaquone-proguanil chemoprophylaxis for 2 weeks after returning home (to complete the 4 weeks required after switching).

Chemoprophylaxis in Special Populations

Long-Term Chemoprophylaxis

Very few studies exist on malaria chemoprophylaxis lasting more than 6 months. No direct data on usage of the newly licensed TQ for more than 6 months exists; a 1-year safety study with detailed ophthalmologic and other safety endpoints is currently enrolling subjects. Persons who have taken 300 mg chloroquine weekly for more than 5 years should be screened twice yearly for early retinal changes. Data indicate no increased risk of serious side effects with long-term use of mefloquine if the drug was tolerated in the short term, although some authorities recommend liver function testing and periodic ophthalmologic examinations for prolonged courses. Available data on long-term use of doxycycline (> 12 months) are limited but reassuring. Atovaquone-proguanil is registered in European countries, with restrictions on duration varying from 5 weeks to 1 year; in the U.K., the 28-day restriction of use has been removed from the Summary of Product Characteristics, and the U.K. guidelines suggest it can be used for up to 1 year. In the U.S., no such restrictions exist. (See Table 5: Long-Term Use of Antimalarial Chemoprophylaxis.) Shoreland and almost all other health authorities do not restrict duration of use.

In the 2 countries in which TQ is licensed, usage is limited to 6 months without specification as to a drug-free interval after which resumption might be permissible. In 1 study that followed ophthalmologic endpoints, benign corneal deposits (vortex keratopathy) not affecting visual acuity were seen in 21% of subjects; these deposits resolved spontaneously after discontinuing TQ, within 12 weeks in 95% of affected subjects and 48 weeks in 100% of subjects. The terminal half-life of TQ of approximately 15 days might make it reasonable to allow for a 12-week “drug holiday” between repeated long-term use of TQ to allow for complete clearance of the drug and resolution of any corneal deposits in almost all affected persons.

TQ may be a preferable option for G6PD normal long-stay travelers with trip durations of ≤ 6 months due to weekly dosing, the intolerability of mefloquine, and the cost of atovaquone/proguanil in many settings. For trips longer than 6 months, mefloquine, if tolerated, remains the drug of choice pending more extensive TQ safety data. Switching drugs during prolonged travel does not appear to be a realistic strategy.

Table 5: Long-Term Use of Antimalarial Chemoprophylaxis

Drug	Licensed Duration in the U.S.	Restrictions on Duration by National or International Bodies[1]	Longest Published Use as Chemoprophylactic Agent
Chloroquine phosphate or chloroquine sulfate (Generics)	No limit	Caution > 5 yrs' duration (retinal toxicity)	30 mos
Mefloquine (Generics)	No limit	No limit	30 mos
Atovaquone-Proguanil (Malarone and generics)	No limit	5 wks to 1 yr in European countries	8 mos as fixed combination; as single agents, 36 mos atovaquone, 36 mos proguanil
Doxycycline (Vibramycin, VibraTabs, Monodox, Adoxa, and other brand names and	4 mos	24 mos (for acne treatment)	12 mos

generics)			
Primaquine (PQ; generics)	No limit	No limit	12 mos
Tafenoquine (TQ)	6 mos	6 mos (Australia; sole other registration)	6 mos

1. Shoreland advises no limit on the duration of use.

Chemoprophylaxis during Pregnancy

Malaria infection in pregnant women may be more severe than in nonpregnant women, and it may increase the risk of adverse pregnancy outcomes, including prematurity, miscarriage, and stillbirth. Pregnant women planning to travel to a malaria risk area may need to consult with a travel medicine expert. They need to maximize personal protective measures to avoid mosquito bites (see *Insect Precautions*) and should take appropriate prescription drugs to prevent malaria. Both CDC and WHO recommend that pregnant women not travel to areas with chloroquine-resistant malaria. Pregnant women should be made aware of this advice.

Neither *mefloquine* nor *chloroquine* has been found to have any harmful effects on the fetus when used in the recommended doses for malaria chemoprophylaxis and can be used during all trimesters of pregnancy. In chloroquine-sensitive areas, pregnant women should preferentially take chloroquine for malaria prevention due to longer experience with this medication. Shoreland (along with all national and international health authorities) advises chloroquine chemoprophylaxis in pregnancy for chloroquine-sensitive areas, although a warning is included in the U.S. package insert.

Atovaquone-proguanil is contraindicated during pregnancy due to lack of data on the safety of the atovaquone component.

Doxycycline should not be used for malaria chemoprophylaxis during pregnancy. However, if no other options are suitable or available, doxycycline may be considered early in pregnancy before tooth and bone formation occurs. The course of doxycycline, including the 4 weeks after travel, must be completed before 15 weeks' gestation. Doxycycline would be indicated in later pregnancy only if required to treat life-threatening infections due to multidrug-resistant *P. falciparum*.

TQ and PQ (see Relapse prevention) are contraindicated during pregnancy because the drug may be passed transplacentally to a G6PD-deficient fetus and cause hemolytic anemia in utero. Whenever radical cure or PART with TQ or PQ is indicated during pregnancy, chloroquine should be given once a week until delivery, at which time TQ or PQ may be given. Females should be advised to avoid getting pregnant for at least 3 months after the last dose of TQ.

Chemoprophylaxis while Breastfeeding

Very small amounts of chloroquine and mefloquine are secreted in breast milk, but the amount of drug transferred is not thought to be harmful to the nursing infant. Because the quantity of the drugs transferred in breast milk is insufficient to provide adequate protection against malaria, infants who require chemoprophylaxis should receive the recommended dosages of antimalarials (see Chemoprophylaxis for Infants and Children, below). More limited data exist for doxycycline, but the same approach is applicable. No information is available on atovaquone-proguanil excretion in breast milk, but because treatment doses of atovaquone-proguanil are recommended for children weighing more than 5 kg, breastfeeding of infants weighing more than 5 kg while taking atovaquone-proguanil is acceptable. Proguanil is excreted into breast milk in small quantities. Whether TQ or PQ are excreted in human breast milk is unknown; therefore, the infant should be tested for G6PD levels if a woman on either medication is breastfeeding. TQ is contraindicated in women who are breastfeeding a G6PD-deficient infant or infant with unknown G6PD status. Likewise, a breastfeeding woman should not breastfeed the aforementioned infants while taking TQ and for 3 months after the last dose of TQ.

Chemoprophylaxis for Infants and Children

All children traveling to malaria risk areas, including young infants, should use personal protective measures to avoid mosquito bites (see *Insect Precautions*), and infants should take antimalarial drugs. The indications for most preventive drugs are the same as for adults; however, it is essential that the correct dosage be used, based on the child's age and/or weight. (See the pediatric dose column in Table 2: Drugs Used in Malaria Prevention.) Young children should avoid travel to areas with chloroquine-resistant *P. falciparum* unless they can take a drug that is highly effective, such as mefloquine, atovaquone-proguanil, primaquine, or doxycycline. Do not give doxycycline to children aged < 8 years (12 years in the U.K.). TQ is not

approved for use in persons aged < 18 years.

Pediatric doses should be calculated carefully according to body weight. Pharmacists can pulverize tablets and prepare gelatin capsules with calculated pediatric doses. Chloroquine and mefloquine should be mixed with something very sweet (such as honey or chocolate sauce) to hide the bitter taste. Atovaquone-proguanil tablets can be crushed and mixed with condensed milk just prior to administration for children who have difficulty swallowing tablets. A room-temperature–stable doxycycline liquid suspension is available and is convenient for children.

Long-stay travelers and expatriates should be advised to adjust the chemoprophylactic dosage according to the increasing weight of the growing child.

For treatment with atovaquone-proguanil, see Standby Emergency Treatment below and the pediatric dose column in Table 7: Prescription Drugs for Self-Treatment of Malaria.

Most antimalarials have narrow toxicity ranges, and an overdose of antimalarial drugs can be fatal in children. Medication should be stored in childproof containers out of children's reach.

Chemoprophylaxis for HIV-Infected Individuals on Antiretrovirals

Malaria prevention is as important for immunocompromised persons as it is for immunocompetent persons. Although malaria does not appear to pose a greater risk for adverse outcomes in HIV-infected travelers (except pregnant women with HIV), antimalarial drug interactions and adverse effects must be considered. Published data are lacking on the safety and clinical efficacy of recommended malaria chemoprophylaxis regimens in the HIV-infected traveler on antiretroviral therapy (ART). Nevertheless, clinically relevant concerns have yet to be shown.

Approach to the Use of Antimalarial Chemoprophylactic Agents

Among the different classes of antiretroviral drugs, older drugs (such as protease inhibitors [PIs]) have potential interactions, whereas newer combinations (such as integrase inhibitor/nucleoside reverse transcriptase inhibitor [NRTI] combinations) have fewer interactions.

Doxycycline is the least likely chemoprophylactic antimalarial to have interactions with a variety of ART regimens, except for efavirenz, which can potentially decrease plasma concentration of doxycycline.

Chloroquine, along with mefloquine, has potential for QTc prolongation when used with some ART regimens, especially PIs and the NNRTI rilpivirine.

Mefloquine is the most likely chemoprophylactic antimalarial to have potential interactions, and it may be prudent for patients on ART regimens to avoid mefloquine, if possible.

Atovaquone and proguanil levels may be lowered by efavirenz, but clinical failure has not been demonstrated. The cautious patient might want to avoid atovaquone-proguanil if on a PI or on a non-nucleoside reverse transcriptase inhibitor (NNRTI) due to potential reduction in antimalarial drug concentrations.

Primaquine’s hemolytic effects can theoretically be increased by efavirenz, although the level of evidence is very low.

Tafenoquine’s potential for drug interaction with ART lack data; therefore, avoid tafenoquine if possible until the drug interactions are established.

Approach to Patients on Common ART Regimens

Beware if a patient is on PIs because these drugs raise the greatest concern for interactions with antimalarial drugs, whereas NRTIs and integrase inhibitors are least likely to interact.

Currently, initial ART therapy is generally recommended to be a combination of an integrase strand transfer inhibitor (InSTI) with 2 nucleoside reverse transcriptase inhibitors (NRTIs). Several once-daily, fixed-dose combinations are commonly used and have no significant interactions with antimalarial drugs.

- Bictegravir/emtricitabine/TAF (Bictarvy)
- Dolutegravir/abacavir/lamivudine (Triumeq)
- Elvitegravir/cobicistat/emtricitabine/TAF (Genvoya)
- Elvitegravir/cobicistat/emtricitabine/TDF (Stribild)

The only exceptions are Genvoya and Stribild, where the cobistat coformulation with elvitegravir may increase mefloquine levels.

The fixed-dose combinations containing the NNRTI rilpivirine, which can potentially prolong the QTc interval, may have a potential weak interaction in this regard with chloroquine and mefloquine but clinical significance is uncertain.

- Dolutegravir/rilpivirine (Juluca)
- Rilpivirine/emtricitabine/TDF (Complera)
- Rilpivirine/emtricitabine/TAF (Odefsy)

Some patients remain on effective and popular combinations of an InSTI with NRTIs, and these also appear to have minimal interactions with malaria chemoprophylaxis drugs:

- Dolutegravir (Tivicay) PLUS emtricitabine/TDF (Truvada) or emtricitabine/TAF (Descovy)
- Raltegravir (Isentress) PLUS emtricitabine/TDF (Truvada) or emtricitabine/TAF (Descovy)

Preexposure prophylaxis with Truvada does not interfere with antimalarials.

Efavirenz/emtricitabine/tenofovir (Atripla): Concurrent use of efavirenz and atovaquone-proguanil or doxycycline or mefloquine may decrease plasma concentrations of the antimalarial agents and possibly lower their efficacy (moderate interaction). Although evidence is very low, efavirenz can theoretically increase the hemolytic effects of primaquine; co-administration with primaquine should be avoided.

Older combinations containing PIs (e.g. lopinavir/ritonavir [Kaletra]) have more interactions with antimalarials, due to possible QTc prolongation, potential reduction of ART concentration by mefloquine, and lower atovaquone and proguanil levels.

Malaria treatment regimens that include artemisinin, lumefantrine, or quinine are much more likely to have safety or efficacy problems, especially with PIs, NNRTIs, and the chemokine receptor (CCR5) antagonist, maraviroc. If any possibility of malaria arises, patients on antiretrovirals need to seek care by an experienced infectious disease specialist.

Drug information and potential interactions between drugs used for malaria chemoprophylaxis and those used in ART regimens can be found at the following resources:

- University of Liverpool website: www.hiv-druginteractions.org
- AIDSinfo website (updated regularly): http://aidsinfo.nih.gov

Chemoprophylaxis for Individuals on Anticoagulants

Travelers taking warfarin or other coumarin derivatives should start any chemoprophylaxis 2 to 3 weeks before travel to malarious areas. A baseline international normalized ratio (INR) should be checked prior to starting chemoprophylaxis and rechecked 1 week after starting chemoprophylaxis to determine whether the warfarin dosage needs to be adjusted. Once chemoprophylaxis has been completed, the INR should be checked again to restabilize anticoagulant therapy.

New oral anticoagulants, such as dabigatran etexilate, rivaroxaban, and apixaban, have a lower potential for drug interactions than do the coumarins, and no clinically significant interactions have occurred.

Travelers on extended trips should monitor their INR with periodic checks at their destination; however, the sensitivity of thromboplastin reagents used in different countries may vary. INR self-testing devices are readily available and can be used safely by experienced patients who may wish to stay in contact with their home anticoagulant clinic for dosage recommendations.

Chemoprophylaxis for Individuals with Epilepsy

Neither chloroquine nor mefloquine should be used for persons with epilepsy.

For areas with a high risk of chloroquine-resistant *P. falciparum*, doxycycline or atovaquone-proguanil can be used. Exceptions to the use of doxycycline include:

- Children aged < 8 years (per U.S. guidelines) should not take doxycycline.
- Because the half-life of doxycycline is reduced by phenytoin, carbamazepine, and barbiturates, it is advisable to use another antimalarial, if possible. If it is not possible or acceptable to the traveler, increase the dose of doxycycline to 100 mg twice daily and counsel regarding measures to minimize the risk of adverse events.

Malaria Medications Overseas

ACTs, such as artemether-lumefantrine (Coartem and generics), are the standard of care for treatment of all species of malaria in most malaria-endemic countries. ACTs have the most rapid onset of action of any available antimalarial drug. Based on limited data in European travelers, the cure rate in nonimmune adult travelers is estimated to be more than 95%. Although

not presently approved in the U.S. for nonfalciparum malaria, artemether-lumefantrine is highly active against all species. The 2015 WHO Malaria Guidelines state that ACTs are drugs of choice for treatment of all species in all countries; however, chloroquine can be used in areas with known chloroquine sensitivity.

Drugs Used for Malaria Treatment Outside the U.S.

Travelers should be aware that the medical management of malaria in countries where the disease routinely occurs may differ from their country of origin. However, in many countries where malaria is endemic, only a limited number of effective medications may be available for treatment. In fact, some of the drugs used may be ineffective for persons, such as travelers, without partial immunity to malaria or may be associated with unacceptable adverse effects.

See also Table 6: Brand Names of Antimalarials Encountered Abroad, below.

Artemisinin Derivatives

Artesunate, artemether, arteether, and dihydroartemisinin are naturally occurring antimalarials derived from the qinghaosu plant and are available in oral, suppository, and injectable forms. Intravenous (IV) artesunate (first-line medication) decreases mortality from *severe* falciparum more effectively than quinine. Artemisinin derivatives have high recrudescence rates (about 10%–50%) when used as monotherapy (e.g., dihydroartemisinin; Cotecxin) and therefore must be used in combination with other drugs such as mefloquine, tetracycline, or lumefantrine. Although some concerns about neurotoxicity in animals exist, no clinical neurological events have been observed in humans to date.

Artemisinin-Based Combination Therapy

ACT is highly efficacious, with Day 28 cure rates generally exceeding 95% (adjusted for reinfection with PCR genotyping), and it costs less than USD1 per adult treatment in endemic areas. Recent data confirm the safety of artemether-lumefantrine (Coartem) in the first trimester of pregnancy; the safety of other ACTs has not been established. In the U.S., Coartem is FDA category C, indicating that use during pregnancy is acceptable only if the potential benefit justifies the potential risk to the fetus. CDC advises use of artemether-lumefantrine in pregnant women in the second and third trimester and in the first trimester if other options are not immediately available.

The following ACT drugs are recommended by WHO for the treatment of uncomplicated malaria (all species):

- **Artemether-lumefantrine (coartemether):** Coartem and Riamet (Novartis)
  - Registered, fixed-dose combination of artemether (20 mg) and lumefantrine (120 mg). Originally developed in China, it is now manufactured by Novartis in China using Western manufacturing standards.
  - This drug is marketed at an industrialized country price in Europe and other nonmalarious countries under the name Riamet (as Coartem in the U.S.) and in 6-dose blister packs for treatment of uncomplicated falciparum malaria as well as for SBET. The same product is available as Coartem in malaria-endemic countries.
  - Artemether-lumefantrine should be taken with food because lumefantrine absorption is enhanced by co-administration of fat.
  - The most frequently reported side effects for a 6-dose adult regimen are headache, asthenia, dizziness, anorexia, myalgia, and arthralgia. The most common adverse reactions in children are fever, cough, vomiting, anorexia, and headache.
  - Delayed hemolytic anemia (generally mild) has been reported in patients with uncomplicated malaria and low parasitemias treated with artemether-lumefantrine. Hematocrit should be monitored weekly for 3 weeks following therapy.
  - Caution should be used when administering this drug to persons with severe hepatic or renal impairment.
  - Although no cardiac issues arose in trials, persons with QTc prolongation, family history of QTc prolongation or sudden death, known electrolyte disturbances, or those on medications with potential to cause QTc interval prolongation (notably macrolide and fluoroquinolone antibiotics and other antimalarial drugs) should not receive artemether-lumefantrine. A large number of other drugs affect the QTc interval, and potential interactions should be investigated carefully. If mefloquine is administered immediately prior to artemether-lumefantrine, decreased exposure to lumefantrine may occur; food consumption should be encouraged while taking artemether-lumefantrine. Artemether-lumefantrine also may reduce the effectiveness of hormonal contraceptives.
  - Coartem Dispersible (Novartis) was developed especially for children with *P. falciparum* malaria; 100 million doses have been delivered to 39 malaria-endemic countries.

- Artemether-lumefantrine is not approved or indicated for the treatment of severe malaria or for malaria chemoprophylaxis.

- **Dihydroartemisinin-piperaquine (DHA-PQP):** Eurartesim (Sigma-Tau/MMV)
  - Was prequalified by WHO and approved by European Medicines Agency (EMA) in 2011 for treatment of uncomplicated *P. falciparum* malaria
  - Made using Good Manufacturing Practice (GMP) and has received the Orphan Drug Designation by U.S. regulatory authorities; see also Standby Emergency Treatment section
  - Currently available in Belgium, Cambodia, France, Germany, Portugal, and U.K.
  - Side effects include anemia, headache, and QTc prolongation
  - Also available as Duo-Cotecxin (Beijing Holley-Cotec Pharmaceuticals) and Artekin (Holleykin Pharmaceuticals), both Chinese-made and not manufactured using GMP; see also Standby Emergency Treatment section
- **Pyronaridine + artesunate:** Pyramax (Shin Poong Pharmaeutical Co Ltd/MMV)
  - For treatment of *P. falciparum* and blood stage *P. vivax* malaria
  - 1 daily dose for 3 days (with or without food) for adults and children weighing more than 20 kg
  - Approved by EMA for use in delineated areas of low malaria transmission with evidence of resistance to artemisinin. Available in Burkina Faso, Burma, Cambodia, Chad, Cote d'Ivoire, South Korea, and Vietnam and expected to be submitted in Thailand.
  - Added to WHO's list of approved medications May 2012
- Other ACTs:
  - **Artesunate-amodiaquine (ASAQ):** ArteSunate AmodiaQuine Winthrop (Sanofi Pasteur)
  - **Artesunate-mefloquine (ASMQ):** Artequin and Artequin Paediatric (Mepha, Acino Switzerland)
  - **Artesunate-sulfadoxine-pyrimethamine (ART-SP)**: Artecospe (Guilin Pharmaceutical Co., China)

IV Artesunate (for severe malaria)

- Recommended by all international and national authorities (WHO, CDC, PHAC, PHE, etc.) as the only first-line treatment of severe malaria in adults and children. This drug is not for SBET use.
- This sole IV drug available for treatment of severe malaria in the U.S. is not FDA-approved but is available from CDC through an expanded investigational new drug (IND) protocol. CDC human subjects approval has been obtained for use, but emergency human subject use approval may still be required by local regulations at some hospitals. Stock is prepositioned at select quarantine stations at major airports across the country and the requesting hospital must arrange for pick-up for local delivery. Drug is often obtainable within several hours in select cities during regular business hours, but delays of up to 24 hours may occur in more peripheral areas or during off hours. Oral antimalarials (artemether-lumefantrine, quinine, or atovaquone-proguanil) may be administered via the oral or nasogastric route while waiting for IV artesunate to arrive. See CDC Malaria Case Management Hotline.
- Available in Canada through the Canadian Malaria Network (CMN; 13 referral centers) in collaboration with Health Canada's Special Access Programme and the Public Health Agency of Canada to facilitate rapid, 24-hour access to this product. Artesunate is sent by courier directly to the attending physician. CMN also stocks intravenous quinine which is a less effective IV agent for severe malaria. See www.canada.ca/en/public-health/services/travel-health/medical-access-artesunate-quinine-malaria-treatment.html.
- Available in Europe and Southeast Asia as Artesunate for Injection (Guilin IV Artesunate), manufactured by Guilin Pharmaceuticals (China). This product has been used in major trials in Africa and Southeast Asia.

Other Drugs Used for Treatment of Malaria

Quinine + Doxycycline

The combination of quinine and doxycycline is a standard malaria therapy and remains an alternative for treatment of *P. falciparum* malaria overseas. The course involves multiple doses over at least 1 week and is frequently associated with adverse events.

Side effects from quinine are common and include tinnitus, dizziness, hearing loss, nausea, headache, and blurred vision. Cardiac conduction disturbances occur occasionally. Gastrointestinal upset is a frequent complication of doxycycline (see Doxycycline for preventive therapy).

Mefloquine

Mefloquine is another treatment alternative overseas but, with the higher doses used for treatment, frequent side effects (hallucinations, psychosis, convulsions) occur in 1:100 to 1:1,500 of those treated with the drug. Shoreland does not recommend the use of treatment doses of mefloquine unless no alternative is available. Mefloquine may be used in all trimesters of pregnancy.

Different Brand Names

Common antimalarials may be known by other brand names abroad.

Table 6: Brand Names of Antimalarials Encountered Abroad

Generic Drug Name	Names That May Be Encountered Abroad
Artemisinin (Quinghaosu) derivatives	
Artemether	Artemedine, Artemotil, Artenam, Artesiane, Artether, Ather, Gvither
Artemether-lumefantrine	Artefan, Coartem, Coartesiane, Combiart, Komefan 140, Lonart, Lufanter, Lumartem, Lumerax, Lumither, Riamet
Artesunate	Allnat, Arthesis, Arinate, Artsuna, Plasmotrim
Artesunate + amodiaquine	Camoquin Plus, Coarsucam
Artesunate (330 or 600 mg) + mefloquine (375 or 750 mg)	Artequin, ASMQ, Mefliam Plus
Artesunate + pyronaridine	Pyramax
Artesunate + sulfadoxine-pyrimethamine	Artecospe
Dihydroartemisinin	Alexin, Artemax, Cotecxin, Cotecxin, Malaxin, Paludose
Dihydroartemisinin (40 mg) + piperaquine (320 mg)	Artekin, Duo-Cotecxin, Eurartesim
Atovaquone-proguanil	Malarone, Malanil
Chloroquine	Avlochlor, Avloquin, Bemaphate, Cadiquin, Chewoquine, Chloroquim, Cloroquina BCN, Cloroquina Fos, Cloroquina Humax, Cidanchin, Ciphaquine, Clip, Difosfato de Cloroquina, Dicloridrato de Cloroquina, Diroquine, Emquin, Genocin, Gontochin, Iroquine, Klorokin, Lariago, Luprochin, Malacin, Malaquin, Malaviron, Malarquine, Maligon, Marachlo, Malarex, Maxipal, Melubron, Mirquin, Nitaquin, Nivaquine, Nuquine, P-Roquine, Quinevite, Resochin, Resochine, Resoquine, Sanoquin, Sinmoquin, Siroquine, Tresochin, Trochin
Mefloquine	Confal, Eloquine, Facital, Lariam, Larimef, Larium, Mafloma, Malacure MF, Mefax, Mefcy, Meff, Meflar, Mefliam, Mefloc, Meflotas, Mefly, Mefque, Meloquine, Mof, Mephaquin, Mevax, MQF, Tramef,
Primaquine	Malirid, Neo-quipenyl, Pimaquine, Primaquina BCN, Primavax, Pmq, Remaquin
Quinine	Alquinn, Cinkona, Dicloridrato de Quinina, Genin, Malakin, Quin-9, Quinarsol, Quinil, Quinimax, Quininat, Quininga, Quinishal, Quinoforme, Surquina, Zequin

Drugs Not Recommended for Prevention or Treatment of Malaria

Chloroquine (Avlochor) + proguanil (Paludrine). For a limited number of chloroquine-resistant countries outside Africa, certain authoritative bodies in France, U.K., and other European nations recommend consideration of chloroquine-proguanil when other drugs are not usable; however, Shoreland no longer recommends this combination for chemoprophylaxis because it has considerably lower efficacy than the drugs recommended above (see Prevention with Chemoprophylaxis) for the prevention of chloroquine-resistant malaria.

Halofantrine (Halfan) is an oral formulation related to mefloquine and quinine that was withdrawn from the market due to concerns about cardiotoxicity. It remains available in the tropics; however, travelers should be aware of the danger of this drug. WHO has reported cardiac deaths associated with the use of halofantrine and does not recommend its use.

Sulfadoxine-pyrimethamine (Fansidar) is an older, toxic, and generally ineffective drug that should not be used for prevention or treatment of malaria in travelers.

Falsified and substandard antimalarial drugs are widely encountered overseas. Travelers should be counseled to carry their own medication and not buy drugs overseas except in an emergency. Additionally, legitimately manufactured drugs made in developing countries may not meet the rigid quality control standards found in developed countries. This is especially true of artemisinin derivatives manufactured in China (except Novartis' coartemether) and Vietnam.

Standby Emergency Treatment

Shoreland recommends either *atovaquone-proguanil* or an *ACT drug* (such as artemether-lumefantrine) as the drug of choice for SBET. Recent data confirm the safety of artemether-lumefantrine (Coartem) in the first trimester of pregnancy, so Shoreland recommends its use throughout pregnancy.

The traveler should stop taking the chemoprophylactic antimalarial while taking the SBET drug.

- Resume the chemoprophylactic drug immediately upon completion of SBET if atovaquone-proguanil will be used for ongoing chemoprophylaxis.
- Resume the chemoprophylactic drug 1 week after *initiating* SBET if another antimalarial (except atovaquone-proguanil) will be used for ongoing chemoprophylaxis.

Table 7: Prescription Drugs for Self-Treatment of Malaria

Drug[1]	Tablet Size	Adult Dose	Pediatric Dose
Artemether-lumefantrine (Coartem in U.S. and Africa; Riamet in Europe)	20 mg artemether and 120 mg lumefantrine	4 tablets (80 mg/480 mg) as a single dose, then 4 tablets again after 8 hrs, then 4 tablets every 12 hrs for 2 days (take with food)	5 kg to < 15 kg: 1 tablet (20 mg/120 mg) as a single dose, then 1 tablet again after 8 hrs, then 1 tablet every 12 hrs for 2 days 15 kg to < 25 kg: 2 tablets (40 mg/240 mg) as a single dose, then 2 tablets again after 8 hrs, then 2 tablets every 12 hrs for 2 days 25 kg to < 35 kg: 3 tablets (60 mg/360 mg) as a single dose, then 3 tablets again after 8 hrs, then 3 tablets every 12 hrs for 2 days ≥ 35 kg: as per adult dose
Atovaquone-proguanil (Malarone and generics; Malanil in South Africa)	Adult: 250 mg atovaquone and 100 mg proguanil Pediatric: 62.5 mg atovaquone and 25 mg proguanil	4 tablets orally once daily for 3 days	5-8 kg: 2 pediatric tablets daily for 3 days 9-10 kg: 3 pediatric tablets daily for 3 days 11-20 kg: 1 adult tablet daily for 3 days 21-30 kg: 2 adult tablets daily for 3 days 31-40 kg: 3 adult tablets daily for 3 days > 40 kg: adult dose
Dihydroartemisinin-piperaquine	Eurartesim in Belgium, Cambodia	Adult: 40 mg dihydroartemisinin and	Up to 75 kg: 3 tablets orally once daily for 3 days	5 to < 7 kg: ½ pediatric tablet (20 mg/160 mg) daily for 3 days

	France, Germany, Portugal, and U.K.	320 mg piperaquine Pediatric: 20 mg dihydroartemisinin and 160 mg piperaquine	75-100 kg: 4 tablets daily for 3 days	7 to < 13 kg: 1 pediatric tablet (20 mg/160 mg) daily for 3 days 13 to < 24 kg: 1 adult tablet (40 mg/320 mg) daily for 3 days 24 to < 36 kg: 2 adult tablets (40 mg/320 mg) daily for 3 days ≥ 36 kg: adult dose
	Artekin in Cambodia	Adult: 40 mg dihydroartemisinin and 320 mg piperaquine	2 tablets twice daily for 2 days (a total of 8 tablets)	Not applicable

1. Use of brand names is for identification only and does not imply endorsement.

Note: For treatment of febrile illness only when professional medical care is not available within 24 hours. Medical care should be sought as soon as possible after self-treatment and the preventive drug should be reinstituted. The self-treatment drug should not be the same as the preventive medication.

In malaria-endemic countries, travelers may have access to a RDT for self-testing along with self-treatment, although RDTs are only approved for laboratory use in the U.S. (see description of BinaxNOW). RDTs may be useful aids for some travelers while in areas distant from reliable medical care, keeping in mind the limitation that many ill travelers are unable to accurately perform or interpret the test.

Atovaquone-Proguanil

Atovaquone-proguanil may be used for self-treatment of malaria if it has not been used for chemoprophylaxis. Treatment doses are associated with nausea, vomiting, abdominal pain, diarrhea, increased transaminases, and rarely, rash and/or seizures. This drug is contraindicated during pregnancy. For persons with severe renal impairment, atovaquone-proguanil can be used with caution for treatment, but only if the benefits of the 3-day treatment regimen outweigh the potential risks of increased drug exposure. Only limited data exist to support the efficacy of atovaquone-proguanil for treatment of nonfalciparum malaria; it appears to have good but not 100% efficacy.

Artemisinin-Based Combination Therapies

ACTs, such as those mentioned above (Coartem, Riamet, and Eurartesim), are considered the preferred choice for falciparum malaria treatment by WHO and most other health authorities.

Low-level artemisinin resistance has been reported along the borders shared by Thailand and Cambodia, Cambodia and Vietnam, and Thailand and Burma, and is suspected in border areas of other countries along the Mekong River, including Burma, Cambodia, China (Guangxi Zhuang Autonomous Region and Yunnan Province), Laos, Thailand, and Vietnam.

Currently, ACTs may still be used effectively in areas of possible resistance to artemisinin. No reports exist of Western travelers with *P. falciparum* malaria acquired in Southeast Asia who have failed any reliably sourced ACT (counterfeit ACTs are common in Southeast Asia). Even local patients with a proven delayed clearance phenotype may still be treated successfully with standard ACT regimens.

IV artesunate is not suitable for SBET.

Other Drugs for Standby Emergency Treatment

Quinine + Doxycycline

As a self-treatment regimen, this combination is effective but complicated, involving multiple doses over at least 1 week and is frequently associated with adverse events. This combination should be reserved for individuals who are likely to be compliant with this complicated regimen.

Mefloquine

Mefloquine should be avoided for self-treatment because of the frequency of side effects (e.g., hallucinations, psychosis, convulsions) associated with the high dosages used for treatment unless no alternative is available. Mefloquine may be used

in all trimesters of pregnancy.

Drug Compatibility

Antimalarials and Oral Typhoid Vaccine

The following antimalarials can be administered concurrently with oral typhoid vaccine Ty21a when the antimalarial is given at doses used for chemoprophylaxis: mefloquine, chloroquine, atovaquone-proguanil, or pyrimethamine-sulfadoxine.

- Specific controlled studies show no effect by atovaquone-proguanil on the antibody response to oral typhoid vaccine.
- Proguanil dosing in the atovaquone-proguanil combination is 100 mg/day for chemoprophylaxis.
- Proguanil, when used alone for chemoprophylaxis (200 mg/day dosing) interferes with the immune response to oral typhoid vaccine and should be administered only if more than 10 days have elapsed since the final dose of oral typhoid vaccine.

The manufacturer of Vivotif advises that other antimalarial agents (those not mentioned above) be administered at least 3 days after the last dose of Ty21a.

Shoreland advises that maintaining a 24-hour interval may be adequate between Ty21a and doxycycline, which has a short half-life.

Antimalarials and Live Attenuated Oral Cholera Vaccine

The manufacturer of Vaxchora (oral live attenuated cholera vaccine [CVD 103-HgR]; PaxVax) advises that Vaxchora should be administered at least 10 days before beginning antimalarial chemoprophylaxis with chloroquine. Other antimalarials do not have interactions with Vaxchora.

Antimalarials and Antacids or Bismuth Subsalicylate

Absorption of doxycycline or chloroquine may be impaired when taken concurrently with antacids or bismuth subsalicylate (Pepto-Bismol); at least 3 hours should elapse between doses of antacids/Pepto-Bismol and doxycycline and at least 4 hours between antacids and chloroquine.

CDC Malaria Case Management Hotline

U.S.-based health care providers needing assistance with the diagnosis, species confirmation, or management of suspected cases of malaria in returning travelers can call the CDC Malaria Hotline at 770-488-7788 (M-F, 8:00 a.m.-4:30 p.m., Eastern Time). For emergency consultation after hours, call: 770-488-7100 and request to speak with a CDC Malaria Branch clinician. Detailed information on malaria diagnosis and management are also available online at www.cdc.gov/malaria. Drug resistance testing and parasite identification do not replace initial diagnostic testing, which must be performed immediately on site. For information on obtaining drug resistance testing, see www.cdc.gov/malaria/features/ars.html.
