REVIEW

KENNETH DARDICK, MD
Connecticut Travel Medicine, Storrs, CT

Educating travelers about malaria: Dealing with resistance and patient noncompliance

ABSTRACT

Malaria is a risk to travelers in many parts of the world. Physicians need to tailor chemoprevention strategies to take into account resistance patterns. Patient education is important, especially for those travelers least likely to comply with prevention strategies. Most travelers who contract malaria do not become ill until they return home, so recognition and treatment are crucial.

KEY POINTS

Health information should be targeted to travelers who are likely to use suboptimal chemoprophylaxis or may be noncompliant with prophylaxis—men and people traveling alone.

Mosquito bed nets, insecticides, insect repellents, and preventive drugs effectively reduce the risk of malaria.

Plasmodia have developed resistance to traditional preventive drugs, including chloroquine and sulfadoxine-pyrimethamine, in vast areas of the world.

Mefloquine (taken weekly), doxycycline (taken daily), and atovaquone-proguanil (taken daily) are the preventive drugs of choice in most areas.

Chloroquine is still effective in Haiti, the Dominican Republic, Central America west of the Panama Canal Zone, Egypt, and most countries in the Middle East; in other areas, plasmodia have gained resistance to it.

This paper was funded by an unrestricted grant provided by Hoffmann-La Roche Inc.

PATIENT INFORMATION
Protecting yourself against malaria, page 480

FOR PHYSICIANS counseling patients going to Africa, Asia, or other tropical areas, the problem of malaria prevention is growing more complex.

Chemoprevention must be tailored to a patient's travel itinerary because of the growing problem of resistance. For instance, chloroquine, once the mainstay of chemoprevention, is no longer effective in Africa, but still is effective in Haiti.

Compliance with chemoprevention is a problem, especially with young travelers and those traveling for more than a month, and physicians need to focus their prevention message to them.

Finally, most travelers who contract malaria do not become ill until they return home, so physicians must know how to recognize and treat the disease.

A WORLDWIDE PROBLEM

Malaria affects approximately 300 million persons worldwide and kills about 1 million people each year.[1] Almost 90% of these deaths occur in sub-Saharan Africa, which has the largest number of cases and where children are the most affected. Malaria is endemic in more than 100 countries and territories (FIGURE 1).

TRAVELERS OFTEN EXPOSED

The risk to a nonimmune traveler of acquiring malaria ranges from a relatively low 0.01% in Central America to 8% in the Solomon Islands.[2]

Many more travelers are exposed to malar-

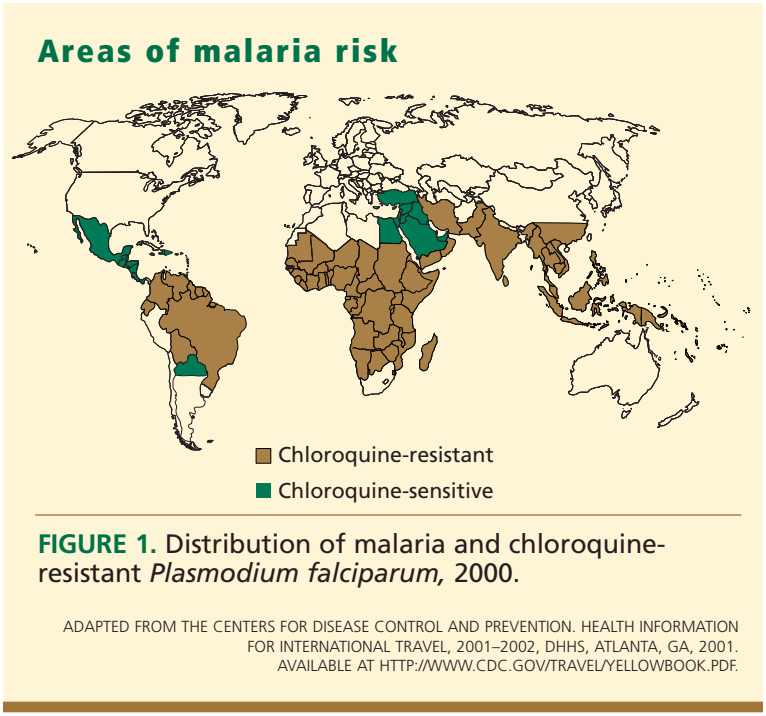

FIGURE 1. Distribution of malaria and chloroquine-resistant *Plasmodium falciparum,* 2000.

ADAPTED FROM THE CENTERS FOR DISEASE CONTROL AND PREVENTION. HEALTH INFORMATION FOR INTERNATIONAL TRAVEL, 2001–2002, DHHS, ATLANTA, GA, 2001. AVAILABLE AT HTTP://WWW.CDC.GOV/TRAVEL/YELLOWBOOK.PDF.

ia without developing symptoms. For example, Jelinek et al[3] found that 48.8% of travelers returning from independent trips to sub-Saharan Africa tested positive for circumsporozoite (CS) antibodies, indicating they had been infected with falciparum malaria. Exposure was much lower in travelers on package tours to the same areas: only 5.6%.

***P vivax* and *P ovale* can remain dormant in the liver for 11 months or more**

LIFE CYCLE OF MALARIA

Humans acquire malaria from the bite of female *Anopheles* mosquitoes infected with plasmodia, a protozoan (**FIGURE 2**). Four species of plasmodia infect humans: *Plasmodium falciparum*, *P vivax*, *P ovale*, and *P malariae*.

Plasmodia have a complex life cycle. They are injected into the blood stream as sporozoites—their infective, motile stage—which travel rapidly from the mosquito saliva to the human liver cells. In the hepatocytes, sporozoites mature to a multinucleated stage capable of asexual reproduction, called tissue schizonts. These contain large numbers of infectious daughters, or merozoites.

Merozoites rupture from the liver cell and pour into the blood stream to invade erythrocytes. Once inside the red blood cells, the parasite matures through a series of asexual erythrocytic stages: ring, trophozoite, and schizont. After 48 to 72 hours, the schizont lyses its host erythrocyte, freeing up to 332 merozoites, which then invade other erythrocytes, thus repeating the cycle. Toxins are released into the blood, making the patient feel sick.

Differences among plasmodia

P falciparum can result in higher levels of parasitemia than the other species of *Plasmodia* because it can invade erythrocytes of all ages. In contrast, *P vivax* and *P ovale* invade only young cells.[4]

On the other hand, *P vivax* and *P ovale* have persistent liver stages, called hypnozoites, that can remain dormant in the liver for 11 months or more. When the hypnozoites finally mature to tissue schizonts and release merozoites, they can cause either a relapse or a delayed primary attack. (A delayed primary attack occurs if the patient was taking chemoprophylactic drugs and did not develop symptomatic parasitemia within 4 weeks after the initial infection.)

No protective immunity

It is important to note that there is no protective immunity to malaria—one can become infected multiple times with the same or other species. However, multiple infection does confer a state of "partial immunity" that attenuates the severity of the infection. In other words, if you are lucky enough to survive your first few infections then you may acquire subsequent infections with minimal symptoms, eg, a slight fever for a few days, but not cerebral malaria.

PREVENTION STRATEGIES

All persons who intend to visit malarious areas should be aware of the risk, know how to help prevent the disease, and understand the importance of obtaining medical attention immediately in the event of fever during or after travel (see **Protecting yourself against malaria,** page 480).

AVOIDING MOSQUITO BITES

The best way to prevent malaria is to avoid exposure to the *Anopheles* mosquito. This is

Life cycle of *Plasmodium*

PHOTO COURTESY OF DR. DICKSON DESPOMMIER.

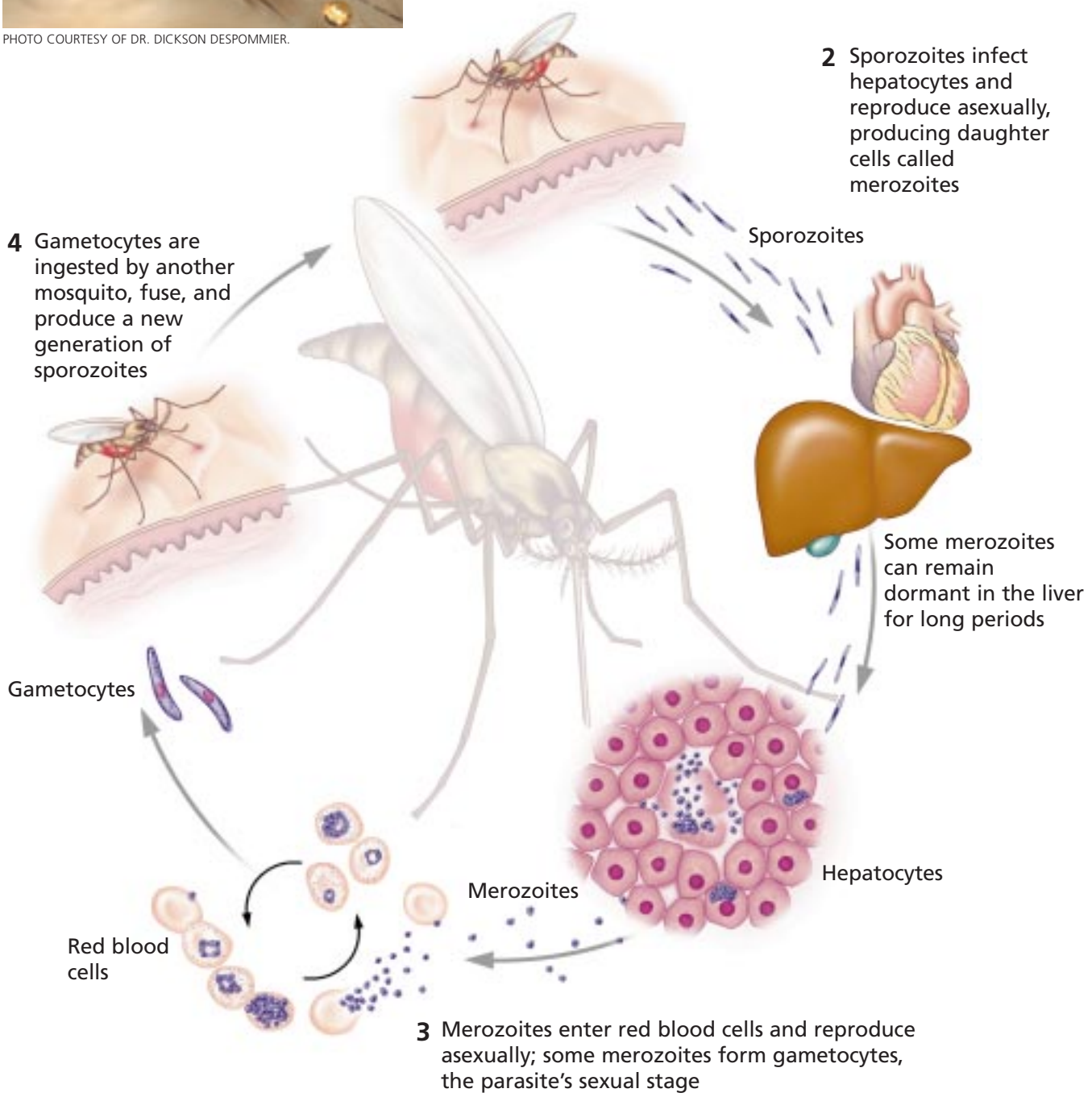

FIGURE 2

TABLE 1

Drugs used in malaria prophylaxis*

Chloroquine (Aralen)
Use: In areas with chloroquine-sensitive *P falciparum*
Adult dose: 300 mg base (500 mg salt) orally, once weekly
Pediatric dose: Base: 5 mg/kg; (salt: 8.3 mg/kg), orally once weekly, up to the maximum adult dose of 300 mg base
Adverse reactions: Mild nausea, blurred vision, headache, psoriasis flare-ups; itching in dark-skinned persons; very rare agranulocytosis, photosensitivity, neuropsychiatric effects
Contraindications: Hypersensitivity to 4-amino-quinolone derivatives; retinal or field changes attributable to drug therapy; psoriasis; use with caution in patients with liver disease or alcoholism

Mefloquine (Lariam)
Use: In areas with chloroquine-resistant *P falciparum*
Adult dose: 228 mg base (250 mg salt) orally, once weekly
Pediatric dose:
< 15 kg: 4.6 mg/kg base (salt: 5 mg/kg) orally once weekly
15–19 kg: 1/4 tab/week
20–30 kg: 1/2 tab/week
31–45 kg: 3/4 tab/week
> 45 kg: 1 tab/week
Adverse reactions: Nausea and vomiting (3%); other adverse reactions (≤ 1%) include abdominal pain, anorexia, arthralgia or myalgia, chills, diarrhea, dizziness, ECG changes, extrasystoles, fatigue, fever, first-degree AV block, headache, skin rash, syncope, or tinnitus
Contraindications: Hypersensitivity to related compounds such as quinine; active depression or a history of seizures or severe psychiatric disorders; use with caution in patients with cardiac conduction abnormalities

Doxycycline (Vibramycin)
Use: Alternative to mefloquine
Adult dose: 100 mg orally, once daily
Pediatric dose: > 8 years of age: 2 mg/kg orally per day up to adult dose of 100 mg
Adverse reactions: Photosensitivity reactions to doxycycline after sunlight (UV) exposure can occur; discontinue at the first sign of erythema; skin reactions can increase when used with sulfonamide, sulfonylureas, or thiazide diuretics
Contraindications: Hypersensitivity to any of the tetracyclines; some commercially available preparations contain sulfites that can result in increased asthmatic attacks in such persons, as well as anaphylaxis

Hydroxychloroquine (Plaquenil)
Use: Alternative to chloroquine
Adult dose: 310 mg base (400 mg salt) orally, once weekly
Pediatric dose: Base: 5 mg/kg (salt: 6.5 mg/kg), orally, once weekly up to maximum adult dose of 310 mg base
Adverse reactions: Same as for chloroquine
Contraindications: Same as for chloroquine

Atovaquone + proguanil (Malarone)
Use: In areas with chloroquine-resistant *P falciparum*
Adult dose: Each tablet contains atovaquone 250 mg/proguanil 100 mg; adults, adolescents, and children ≥ 3 years of age weighing > 40 kg: 1 tablet orally once daily
Pediatric dose: Each pediatric tablet contains atovaquone 62.5 mg/proguanil 25 mg
≥ 3 yrs old and 31–40 kg: 3 oral tablets once daily
≥ 3 yrs old and 21–30 kg: 2 oral tablets once daily
≥ 3 yrs old and 11–20 kg: 1 oral tablet once daily
< 3 years of age or < 11 kg: safety and efficacy have not been established
Adverse reactions: Abdominal pain, nausea, vomiting, headache, diarrhea, asthenia, anorexia, dizziness, pruritus
Contraindications: any known hypersensitivity to proguanil or atovaquone

*Refer to the manufacturer's complete product information for additional descriptions of these agents

sometimes difficult because many accommodations in tropical and subtropical countries lack window screens.

Mosquito bed nets can be useful, particularly if the net is treated every 6 months with permethrin (300–500 mg/m^2) or deltamethrin.[5]

Insect repellents. Use of insect repellents on exposed skin should be encouraged. Those containing *N,N*-diethyl-3-methylbenzamide (DEET) are the most effective. High concentrations of DEET are not necessary for effective protection. Hour Guard, a 35% DEET polymer formulation (3M Corporation, St. Paul, MN) provides up to 12 hours of protection, depending on the species of mosquito and environmental conditions.[6] DEET-based repellents used in combination with permethrin-treated clothing can provide nearly complete protection against mosquito bites.[6]

Concerns about the neurotoxicity of DEET in children are generally misplaced. Fourteen cases of encephalopathy have been

reported, 13 in children younger than 8 years; all but three of the children recovered without sequelae. Most had used DEET long-term, in excessive amounts, or otherwise inappropriately.[6]

As with any product, the labeling and instructions should be read and understood before use.

Staying inside at night. The *Anopheles* mosquito feeds from dusk to dawn. The risk of malaria is reduced by limiting evening exposure to mosquitoes, or, if traveling from a malaria-free urban area to the malarious countryside on day trips, returning to the city before dusk.[7]

CHEMOPROPHYLAXIS

Most travelers to high-risk, malaria-endemic areas should also take a preventive drug (TABLE 1).[8,9] The decision to give a chemoprophylactic drug (and which one to give) depends on:

- Expected exposure to malaria
- Expected exposure to drug-resistant *P falciparum*
- The availability of prompt medical care should malaria occur
- Any contraindications to a chemoprophylactic agent.

The most commonly prescribed drugs in the United States for preventing malaria are chloroquine (Aralen), mefloquine (Lariam) doxycycline (Vibramycin), and the combination drug atovaquone and proguanil (Malarone). The combination of sulfadoxine and pyrimethamine is no longer used for chemoprophylaxis and is reserved for presumptive therapy in the event of febrile illness.

Since November 2000, the Centers for Disease Control and Prevention (CDC) has recommended mefloquine, atovaquone-proguanil, or doxycycline for malaria chemoprophylaxis in areas with chloroquine-resistant malaria. Chloroquine combined with proguanil is no longer recommended.[10]

Recently updated maps identifying risk areas are available from many sources on the Internet:

- The CDC at **www.cdc.gov**
- The World Health Organization (WHO) at **www.who.int**
- The International Society of Travel Medicine at **www.istm.org**
- The Malaria Foundation International at **www.malaria.org**.

We have included a list of our recommendations for chemoprevention regimens in commonly visited countries (TABLE 2).

TABLE 2

Malaria prophylaxis, by destination

DESTINATION	MEDICATION
Africa	Mefloquine or atovaquone-proguanil
Asia	Mefloquine (except Thailand, Myanmar, Cambodia) or atovaquone-proguanil
Cambodia	Doxycycline or atovaquone-proguanil
Caribbean	Chloroquine
Central America (west of the Panama Canal)	Chloroquine
Dominican Republic	Chloroquine
Egypt	Chloroquine
Haiti	Chloroquine
India	Mefloquine or atovaquone-proguanil
Middle East	Chloroquine
Myanmar	Doxycycline or atovaquone-proguanil
South America	Mefloquine or atovaquone-proguanil
Thailand	Doxycycline or atovaquone-proguanil

Chloroquine

Chloroquine inhibits the parasite's production of heme, a toxic byproduct of hemoglobin digestion.[11] It has been the principal antimalarial drug in use worldwide for almost 50 years.

However, *P falciparum* has become resistant to chloroquine in many areas of the world (FIGURE 1). Resistance to chloroquine (and to sulfadoxine-pyrimethamine) is widespread in sub-Saharan Africa, Thailand, Myanmar, Cambodia, and the Amazon basin area of South America. Other chemoprophylactic agents should be considered for travelers to these countries. The drug is still effective in Haiti, the Dominican Republic, Central America west of the Panama Canal Zone, Egypt, and most countries in the Middle East.[9]

***P falciparum* has become resistant to chloroquine in many countries**

Hydroxychloroquine

Hydroxychloroquine is used less often than chloroquine and carries the same potentially severe adverse reactions. It is not effective against chloroquine-resistant *Plasmodia*. Both hydroxychloroquine and chloroquine are contraindicated in patients with any ocular disease, especially retinal diseases such as macular degeneration. Retinopathy has been reported with long-term use of these drugs. They should be used cautiously in patients with hepatic disease or alcoholism.

Mefloquine

Mefloquine kills schizonts in the blood, but its exact mechanism of action is not known.[12] It has superseded chloroquine as the standard antimalarial chemoprophylactic agent, and the CDC recommends it for travelers to most regions where *Plasmodia* is resistant to chloroquine.[10] However, resistance to mefloquine has been confirmed in limited areas of Thailand and the western provinces of Cambodia, with possible mefloquine-resistant strains in the Amazon Basin.[10,13,14]

Mefloquine has a half-life of about 3 weeks and is highly effective in preventing malaria caused by *P falciparum* and *P vivax*.[15] Taking a 250-mg mefloquine tablet once weekly has resulted in a 91% prophylactic effectiveness in East Africa, 99.8% in sub-Saharan Africa, and 100% in the Indonesian province of Irian Jaya.[12,16,17]

Concerns about DEET neurotoxicity in children are generally misplaced

Italian soldiers deployed to Mozambique who received a combination of chloroquine and proguanil experienced 17 cases of malaria per 1,000 soldiers per month.[18] When the combination was replaced by mefloquine, the rate dropped to 1.8.

Neuropsychiatric adverse reactions associated with mefloquine include psychosis, confusion, depression, and hallucinations, as highlighted in case reports.[19–21] Weinke et al[22] calculated the incidence of mefloquine-related neuropsychiatric side effects as 1 in 8,000 among patients who took the drug as therapy for malaria, and 1 in 13,000 among those using it for chemoprophylaxis.

In multiple clinical trials, rates of serious neuropsychiatric reactions were not significantly greater with prophylactic dosages of mefloquine than with alternative agents.[23] Milder neuropsychiatric effects such as vivid dreams, insomnia, and vertigo are seen more commonly with mefloquine than with the combination atovaquone and proguanil.[24]

Nonetheless, patients with active neuropsychiatric conditions need to be monitored when using mefloquine for long periods, and they should not take mefloquine to prevent malaria if they have active depression, a history of seizures, or severe psychiatric disorders.[25] Since 70% of such problems occur within the first three doses, travelers should start taking mefloquine before they depart, making them less likely to stop taking the drug on their own because of side effects and go without any chemoprevention whatsoever.[26]

Patients should take mefloquine with food, as food increases its bioavailability without affecting its elimination half-life.[27] Concurrent use of mefloquine and chloroquine, quinine, or quinidine may result in an increased risk of seizures and electrocardiographic abnormalities.[24]

Doxycycline

Doxycycline attacks the parasite both in the liver and in the red blood cells by preventing its ribosomes from producing proteins.[28] It is effective against multidrug-resistant *P falciparum* and is the most effective prophylactic drug for travelers to malaria-endemic areas of Thailand bordering Myanmar and Cambodia.[10] However, in a study in American troops in Somalia, the attack rate of falciparum malaria was five times higher among users of doxycycline than among users of mefloquine.[29,30]

Doxycycline can cause photosensitivity; therefore, sunscreens and protective clothing are needed during the daylight hours. Daily dosing is necessary because of its relatively short half-life of 16 hours.

Proguanil

Proguanil inhibits dihydrofolate reductase, disrupting the ability of the parasite to synthesize nucleic acids in its pre-erythrocytic phase.[28] Proguanil has been used since the mid-1940s, but when used alone has an effectiveness of only slightly more than 50%.[23] A regimen of proguanil once a day plus chloroquine once a week is more effective, but still

much less effective than other alternatives. This drug is not available in the United States.

Atovaquone-proguanil

Atovaquone prevents parasite replication by selectively inhibiting mitochondrial electron transport.[30] A new combination of atovaquone and proguanil (Malarone) is reported to act synergistically against blood parasites, although the exact mechanism of this synergy is unknown.[31]

The atovaquone-proguanil combination is effective against early liver stages of malaria and is therefore an effective prophylactic. However, it is not effective in killing the hypnozoite stage of *P vivax* or *P ovale*. Therefore, travelers still need to take primaquine as "terminal prevention" after returning home if they have had extensive exposure to these strains of malaria.

In studies of atovaquone-proguanil as chemoprophylaxis against *P falciparum*, the effectiveness rates ranged from 95% to 100% in semi-immune subjects.[32–34]

A study in nonimmune travelers compared atovaquone-proguanil with chloroquine-proguanil.[35] Most people experienced at least one adverse reaction with either combination, although those taking atovaquone-proguanil had significantly fewer gastrointestinal problems. Both combinations were almost 100% effective.

Another study in nonimmune travelers compared atovaquone-proguanil (taken once daily) with mefloquine (taken once a week). The drugs were equally effective, but side effects were fewer and less severe with atovaquone-proguanil.[24]

Atovaquone should be taken with meals. If the patient has difficulty with this, consider alternate treatment. Patients with certain types of gastrointestinal disease may have decreased atovaquone absorption.

Primaquine as terminal prevention

Certain *Plasmodium* species (*P vivax* and *P ovale)* are known to produce relapsing malaria infections years after a person has left a malarious country or has stopped taking preventive malaria medication. For this reason, the CDC advises that travelers who have had prolonged exposure to malaria (for example, Peace Corps workers or missionaries) should consider using primaquine to kill the dormant liver stage (hypnozoite) of the malaria parasite.

Primaquine must not be used in those deficient in G6PD enzyme, owing to the risk of hemolytic anemia. A test for G6PD is mandatory before taking primaquine.[10] The standard adult dose of primaquine is 15 mg base (26.3 mg salt) once daily for 14 days after leaving the malarious area.

When to start, when to stop

Each antimalarial drug is taken on a specific schedule based on its pharmacokinetic and antiplasmodial properties.

Chloroquine should be started 2 weeks before departure and continued for 4 weeks after return.

Mefloquine should be started 1 week before departure and continued for 4 weeks after return.

Doxycycline should be started 1 to 2 days before departure and continued for 4 weeks after return.

Atovaquone-proguanil should be started 1 to 2 days before departure and continued for 1 week after return.

Mefloquine has replaced chloroquine as the standard antimalarial preventive drug

SPECIAL POPULATIONS

Nursing infants

Minute amounts of antimalarial drugs are secreted in breast milk. This is not believed to be toxic to the nursing infant. However, if this is a concern, a decision should be made to discontinue either the drug or the breast-feeding. The importance of the drug to the mother must be considered.

The amount of antimalarial drug secreted in breast milk is not enough to prevent malaria in the infant; therefore, infants who require protection against malaria need to receive antimalarial drugs in recommended doses (TABLE 1).

Infants and children

Severe malaria is common among infants and children in areas where transmission is intense, so chemoprophylaxis is essential for children of all ages.

According to the CDC, mefloquine is

well tolerated by infants weighing less than 15 kg (6.8 lb) and can be used in children who are traveling to regions with chloroquine-resistant *P falciparum*.[10] Experience is limited in infants younger than 3 months and weighing less than 5 kg, and the safety of mefloquine has not been established in those younger than 6 months.

Atovaquone-proguanil is available in a pediatric tablet for children weighing 11 kg or more. Doxycycline is contraindicated in children younger than 8 years. Chloroquine remains the agent of choice in areas with chloroquine-sensitive malaria.

Giving proper doses of antimalarial medication to children can be difficult. No liquid preparations of commonly used antimalarial medications are available in the United States. Chloroquine and mefloquine are bitter. If the tablets are crushed, the bitter taste must be masked by mixing the powder with sweet syrup or by placing it in food or a capsule. These extemporaneous dosing forms are not approved by the US Food and Drug Administration but are widely used; to ensure accurate dosing, a pharmacist should prepare them.

Contraindications to mefloquine:
Depression
Seizures
Severe psychiatric disorders

HIV-infected patients

Many HIV-infected persons travel from temperate zones to tropical and subtropical destinations.[36] While concern about opportunistic infections in HIV-positive persons is justified, research does not indicate a biological link between malaria and HIV infection. Malaria is not an opportunistic infection, is not exacerbated by HIV (as are toxoplasmosis and cryptosporidiosis), and does not hasten the clinical progression of HIV infection.[37,38]

Generally, most HIV-infected travelers have a low risk of severe health problems if they adhere to the same sound medical advice given to HIV-negative travelers. However, one needs to anticipate HIV-specific immigration issues, the medical resources available abroad, and problems regarding travel with multiple medications.

In addition, when prescribing specific chemoprophylactic agents, you need to consider the stage of immunodeficiency and drug interactions with antiretroviral drugs. For example:

- Didanosine may decrease the bioavailability of doxycycline, owing to the buffering agents used in didanosine tablets or powder.[25] Delayed-release didanosine capsules do not contain a buffering agent and would not be expected to interact with tetracycline antibiotics.
- The combination of lopinavir and ritonavir decreases the plasma levels of atovaquone. The clinical significance is unknown, but an increase in atovaquone dosage may be required.
- Rifampin (used to treat tuberculosis, an opportunistic infection in HIV-infected patients) is a potent inducer of the cytochrome P450 hepatic enzyme system and can reduce the plasma concentrations and possibly the efficacy of atovaquone.[25]
- Sulfadoxine and pyrimethamine should not be used concurrently with sulfamethoxazole-trimethoprim (used in *Pneumocystis carinii* prophylaxis) or other sulfonamides, because the adverse effects of the drugs may be additive.[25]
- In vitro data involving mefloquine indicate that the formation of its metabolite may be inhibited by drugs metabolized by the cytochrome P450 3A4 isoenzyme, such as the protease inhibitors indinavir and nelfinavir.[39] However, pharmacokinetic profiles of HIV-infected patients who took mefloquine for malaria chemoprophylaxis show that the metabolism of mefloquine was not inhibited by the protease inhibitors.[40]

COMMON ERRORS

Studies of Western travelers who contracted malaria reveal several common errors: they didn't take precautions to avoid mosquito bites, they didn't take a preventive drug, or they received an ineffective drug (eg, chloroquine in an area of chloroquine resistance).

Muehlberger et al[41] studied 51 German travelers who contracted malaria in Kenya and found that ineffective chemoprophylaxis and lack of prophylaxis were the principal reasons. Ineffective chemoprophylaxis was primarily the result of inappropriate medical advice (88%). Most patients (58%) who did not comply with medical advice did so because of carelessness or concern about side

TABLE 3

Malaria risk factors for nonimmune travelers

RISK FACTORS	MOST RISKY	LESS RISKY
Destination	Africa	Central and South America
Local traveling	Rural areas	Urban areas
Type of accommodations	Camping	Well-screened or air-conditioned rooms
Duration of stay	> 4 weeks	1–4 weeks
Times of travel	Local season of high malaria transmission (rainy season)	Local season of low malaria transmission (dry season)
Destination elevation	< 2000 meters	> 2000 meters
Preventive measures	No chemoprophylaxis No personal protective measures	Use of preventive drugs and treated bed nets
Travel companions	None or nonfamily members*	Family members or partners
Gender	Males†	Females
Malaria knowledge	Insufficient	Sufficient

*Those who travel alone or with friends have a 2.6-fold higher risk of infection than those traveling with family members or partners
†Men have been reported to have twice the risk of women

HEALTH INFORMATION FOR INTERNATIONAL TRAVEL, 1996–1997. ATLANTA: U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, PUBLIC HEALTH SERVICE, CENTERS FOR DISEASE CONTROL AND PREVENTION, NATIONAL CENTER FOR INFECTIOUS DISEASES, DIVISION OF QUARANTINE, 1997; HHS PUBLICATION NUMBER 95-8280; KAIN KC, KEYSTONE JS. MALARIA IN TRAVELERS. EPIDEMIOLOGY, DISEASE, AND PREVENTION. INFECT DIS CLIN NORTH AM 1998; 12:267–284; SCHLAGENHAUF P. MEFLOQUINE FOR MALARIA CHEMOPROPHYLAXIS 1992–1998. J TRAVEL MED 1999; 6:122–133.

effects. Diagnosis and medical care were unnecessarily delayed in 28% of cases; this was primarily due to failure to examine blood smears in a timely manner. The researchers concluded that 94.5% of cases associated with inappropriate medical advice could have been prevented by giving an effective prophylactic medication.

The CDC[42] has reported 4,685 cases of imported malaria in American travelers between 1992 and 2001 (not counting military personnel and non-US citizens). Of these patients, 19% had received an inappropriate chemoprophylactic regimen and 56% took no chemoprophylactic medication. The most common inappropriate chemoprophylaxis was chloroquine in areas with known chloroquine resistance. During January through March 2001, two American citizens died of malaria after taking chloroquine alone or chloroquine plus proguanil in countries with chloroquine-resistant malaria.

Who is least compliant?

Lobel et al[43] recently surveyed travelers returning to North America and Europe from Africa and found that 97% were aware of the risk of malaria and more than 90% received medical advice before going. More than 95% used chemoprophylaxis, but only 62% used both regular chemoprophylaxis and two or more antimosquito measures. Adherence to drug therapy was lowest for travelers:

- Who took a daily medication rather than a weekly one
- Who believed they had an adverse event related to the drug
- Younger than 40 years
- Traveling for more than 1 month.

About 95% of the Americans were taking an effective regimen, ie, mefloquine or doxycycline. Adverse events were judged to have a smaller impact on adherence than the dosing schedule. The authors concluded that health information should be targeted to travelers

Common errors:
No precautions
No drug
Wrong drug

who are likely to use suboptimal chemoprophylaxis or may be noncompliant with prophylaxis (TABLE 3).

MONITORING FOR DISEASE SYMPTOMS

No antimalarial prophylactic regimen guarantees complete protection. Because approximately 90% of travelers who contract malaria do not become ill until returning home, it is up to us—in an area where malaria is not common—to recognize malaria, make the laboratory diagnosis, and treat it.[44,45]

About 1,500 cases of malaria are diagnosed in the United States each year, 99.7% in travelers.[10] Approximately 90% of travelers who contract malaria become ill after returning home.[46] In addition, each year a few cases of malaria result from blood transfusions, from congenital infections, or from transmission by locally infected mosquitoes.[16]

When symptoms of malaria are recognized early, several effective treatments exist. When appropriate medical care is delayed, however, complications can ensue, such as renal failure, coma, and even death. The fatality rate of malaria in nonimmune travelers may be as high as 8.7%,[47] although much lower rates are usually reported.[44]

Travelers should know that they can contract malaria both during the trip (as quickly as 6 days following initial exposure) or several months and even longer after they return home.[8]

Symptoms that could indicate malaria include:

- Myalgia
- Fever
- Headache
- Chills

Although a fever that develops during the first week of travel is rarely due to malaria, any elevated temperature should be treated as a medical emergency and the traveler should request a laboratory test for malaria. Blood smears should be repeated at least three times in 72 hours, as a single negative smear might fail to reveal the parasites that are released periodically.[48]

Parents should know that malaria can cause flulike symptoms in children up to a year after traveling in a malarious region.[9] Such symptoms must be assessed by a health care professional at once.

REFERENCES

1. **World Health Organization.** Malaria, 1982–1997. WHO Weekly Epidemiological Record 1999; 74:265–270.
2. **Steffen R, Fuchs E, Schildknecht J, et al.** Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting east Africa. Lancet 1993; 341:1299–1303.
3. **Jelinek T, Loscher T, Nothdurft HD.** High prevalence of antibodies against circumsporozoite antigen of *Plasmodium falciparum* without development of symptomatic malaria in travelers returning from sub-Saharan Africa. J Infect Dis 1996; 174:1376–1379.
4. **Krogstad DJ.** Plasmodium species (malaria). In: Mandell GL, Dolin R, Bennett JE (editors). Principles and Practice of Infectious Disease, 4th ed. New York: Churchill Livingstone; 1995:2415–2427.
5. **Nevill CG, Some ES, Mung'ala VO, et al.** Insecticide-treated bednets reduce mortality and severe morbidity from malaria among children on the Kenyan coast. Trop Med Int Health 1996; 1:139–146.
6. **Fradin MS.** Mosquito and mosquito repellents: a clinician's guide. Ann Intern Med 1998; 128:931–940.
7. Health Information for International Travel, 1996–97. Atlanta: US Dept of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Infectious Diseases, Division of Quarantine, 1997; HHS publication no. 95-8280.
8. **World Health Organization.** Malaria risk for travelers to Africa. WHO Weekly Epidemiological Record 2001; 76:25–27.
9. **Centers for Disease Control and Prevention.** Malaria: General information. 2001. Available at http://www.cdc.gov/travel/malinfo.htm.
10. **Centers for Disease Control and Prevention.** Health Information for International Travel, 2001–2002, DHHS, Atlanta, GA, 2001. Available at http://www.cdc.gov/travel/yellowbook.pdf.
11. **Slater AF, Cerami A.** Inhibition by chloroquine of a novel haem polymerase enzyme activity in malaria trophozoites. Nature 1992; 355:167–169.
12. **Ohrt C, Richie TL, Widjaja H, et al.** Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1997; 126:963–972.
13. **Hopperus Buma AP, van Thiel PP, Lobel HO, et al.** Long-term malaria chemoprophylaxis with mefloquine in Dutch marines in Cambodia. J Infect Dis 1996; 173:1506–1509.
14. **Chia JK, Nakata MM, Co S.** Smear-negative cerebral malaria due to mefloquine-resistant *Plasmodium falciparum* acquired in the Amazon. J Infect Dis 1992; 165:599–600.
15. **Palmer KJ, Holliday SM, Brogden RN.** Mefloquine. A review of its antimalarial activity, pharmacokinetic properties and therapeutic efficacy. Drugs 1993; 45:430–475.
16. **Centers for Disease Control and Prevention.** Malaria surveillance—United States. MMWR 2001; 50(SS01):25–44. Available at **http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5001a2.htm**.
17. **Lobel HO, Miani M, Eng T, Bernard KW, Hightower AW, Campbell CC.** Long-term malaria prophylaxis with weekly mefloquine. Lancet 1993; 341:848–851.
18. **Peragallo MS, Sabatinelli G, Majori G, Cali G, Sarnicola G.** Prevention and morbidity of malaria in nonimmune subjects; a case-control study among Italian troops in Somalia and Mozambique, 1992–1994. Trans R Soc Trop Med Hyg 1997; 91:343–346.
19. **Winstanley P.** Mefloquine: the benefits outweigh the risks. Br J Clin Pharmacol 1996;42:411–413.
20. **Croft AM, World MJ.** Neuropsychiatric reactions with mefloquine chemoprophylaxis. Lancet 1996; 347:326.
21. **Dawood R.** The Lariam effect. Condé Nast Traveler 1996; 31:20.
22. **Weinke T, Trautmann M, Held T, et al.** Neuropsychiatric side effects after the use of mefloquine. Am J Trop Med Hyg 1991;45:86–91.
23. **Lobel HO, Kozarsky PE.** Update on prevention of malaria for travelers. JAMA 1997; 278:1767–1771.
24. **Overbosch D, Schilthuis H, Bienzle U, et al.** Atovaquone-proguanil versus

mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study. Clin Infect Dis 2001; 33:1015–1021.
25. **McEvoy GK, Litvak K, Welsh OH, et al (editors).** American Hospital Formulary Service Drug Information 2001. Bethesda, MD: American Society of Health-System Pharmacists; 2001.
26. **Bradley DJ, Warhurst DC.** Malaria prophylaxis: guidelines for travelers from Britain. Malaria Reference Laboratory of the Public Health Laboratory Service, London. BMJ 1995; 310:709–714.
27. **Crevoisier C, Handschin J, Barre J, Roumenov D, Kleinbloesem C.** Food increases the bioavailability of mefloquine. Eur J Clin Pharmacol 1997;53:135–139.
28. **Juckett G.** Malaria prevention in travelers. Am Fam Physician 1999; 59:2523–2530.
29. **Wallace MR, Sharp TW, Smoak B, et al.** Malaria among United States troops in Somalia. Am J Med 1996; 100:49–55.
30. **Fry M, Pudney M.** Site of action of the antimalarial hydroxynaphthoquinone, 2-[trans-4-(4′-chlorophenyl) cyclohexyl]-3-hydroxy-1,4-naphthoquinone (566C80). Biochem Pharmacol 1992; 43:1545–1553.
31. **Canfield CJ, Pudney M, Gutteridge WE.** Interactions of atovaquone with other antimalarial drugs against *Plasmodium falciparum* in vitro. Exp Parasitol 1995; 80:373–381.
32. **Shanks GD, Gordon DM, Klotz FW, et al.** Efficacy and safety of atovaquone/proguanil as suppressive prophylaxis for Plasmodium falciparum malaria. Clin Infect Dis 1998; 27:494–499.
33. **Lell B, Luckner D, Ndjave M, Scott T, Kremsner PG.** Randomised placebo-controlled study of atovaquone plus proguanil for malaria prophylaxis in children. Lancet 1998; 351:709–713.
34. **van der Berg JD, Duvenage CS, Roskell NS, Scott TR.** Safety and efficacy of atovaquone and proguanil hydrochloride for the prophylaxis of Plasmodium falciparum malaria in South Africa. Clin Ther 1999; 21:741–749.
35. **Hogh B, Clarke PD, Camus D, et al.** Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in nonimmune travellers: a randomised, double-blind study. Malarone International Study Team. Lancet 2000; 356:1888–1894.
36. **Oehler T, Buchel B, Hatz C, Furrer H.** [Advice to HIV infected persons traveling to tropical or subtropical destinations]. Schweiz Med Wochenschr 2000; 130:1041–1050.
37. **Nwanyanwu OC, Kumwenda N, Kazembe PN, et al.** Malaria and human immunodeficiency virus infection among male employees of a sugar estate in Malawi. Trans R Soc Trop Med Hyg 1997; 91:567–569.
38. **Ariyoshi K, Berry N, Wilkins A, et al.** A community-based study of human immunodeficiency virus type 2 provirus load in rural village in West Africa. J Infect Dis 1996; 173:245–248.
39. **Bangchang KN, Karbwang J, Back DJ.** Mefloquine metabolism by human liver microsomes. Effect of other antimalarial drugs. Biochem Pharmacol 1992; 43:1957–1561.
40. **Schippers EF, Hugen PW, den Hartigh J, et al.** No drug-drug interaction between nelfinavir or indinavir and mefloquine in HIV-1-infected patients. AIDS 2000; 14:2794–2795.
41. **Muehlberger N, Jelinek T, Schlipkoeter U, von Sonnenburg F, Nothdurft HD.** Effectiveness of chemoprophylaxis and other determinants of malaria in travelers to Kenya. Trop Med Int Health 1998; 3:357–363.
42. **Centers for Disease Control and Prevention.** Malaria deaths following inappropriate malaria chemoprophylaxis United States, 2001. MMWR 2001; 50:597–616.
43. **Lobel HO, Baker MA, Gras FA, et al.** Use of malaria prevention measures by North American and European travelers to East Africa. J Travel Med 2001; 8:167–172.
44. **Freedman DO.** Imported malaria—here to stay. Am J Med 1992; 93:239–242.
45. **Kain KC.** Chemotherapy of drug-resistant malaria. Can J Infect Dis 1996; 7:25.
46. **Kain KC, Keystone JS.** Malaria in travelers. Epidemiology, disease, and prevention. Infect Dis Clin North Am 1998; 12:267–284.
47. **Schlagenhauf P.** Mefloquine for malaria chemoprophylaxis 1992–1998. J Travel Med 1999; 6:122–133.
48. **Centers for Disease Control and Prevention.** Malaria surveillance—1998. MMWR 2001; 50(SS05);19–20.

ADDRESS: *Kenneth Dardick, MD, Connecticut Travel Medicine, 34 Professional Park Road, Storrs, CT 06268; e-mail kdardick@dardick.com.*