In increases in international travel are resulting in a growing number of travelers at risk for malaria, with Plasmodium vivax being the most common cause of late-onset malaria. In a recent review of data on travelers from Israel and the United States, more than one third of malaria-infected travelers developed illness more than 2 months after their return, the majority of cases were due to P vivax and Plasmodium ovale. Sixty percent of patients had taken appropriately effective blood-stage prophylaxis, with mefloquine being the most commonly used drug.\(^1\) Chloroquine-resistant Plasmodium falciparum is present throughout Africa, Asia, and South America, and in parts of Southeast Asia, multidrug-resistant P falciparum is frequent. Chloroquine-resistant P vivax is also an important health threat in certain parts of the world, mainly in Asia. Randomized trials have demonstrated that atovaquone–proguanil hydrochloride (A/P, Malarone\(^\text{TM}\), GlaxoSmithKline) is safe and effective for prevention and treatment of malaria caused by P falciparum and has few adverse effects.\(^2\) There are limited data regarding the efficacy of prophylaxis against non–P falciparum malaria infections. Probably, it has limited activity against P vivax–established hypnozoites as was observed in an open-label study conducted in Thailand, where treatment with A/P did not prevent relapses of this species.\(^3\) There are only a handful of case reports on Western travelers with malaria caused by P vivax or P ovale in spite of A/P prophylaxis.\(^2,4,5\)

Two cases of tertian malaria in travelers taking A/P for prophylaxis are presented.

**Case 1**

A 56-year-old man had traveled to Madagascar, Tanzania, and India in 2002; he did not take any antimalarial prophylaxis and was diagnosed with malaria due to P falciparum that same year. He received treatment with mefloquine and pyrimethamine-sulfadoxine (PS). In October 2004, he traveled to Papua New Guinea for 1 month and took A/P as prophylaxis, following the standard recommendations. Two and a half months after his return, he presented to our hospital with a 3-day history of fever over 40°C, chills, myalgia, headache, and non-specific abdominal pain. On admission, his temperature was 41°C and his physical examination was normal. Laboratory tests only showed a low total platelet count, at 114,000/mL, and values for hemoglobin, leukocytes, liver function tests, lactate dehydrogenase, and total bilirubin, and urine and...
Electrolytes were normal. The thick and thin blood films showed *P. vivax* parasites, with a 0.1% parasite density. Seminested multiplex polymerase chain reaction (PCR) assay confirmed the diagnosis. Genome amplification and sequencing of the *P. vivax* CYT *b* gene (DNeasy Tissue Kit from QIAGEN, Hilden, Germany) found no mutations previously associated with resistance to A/P. Due to the possibility of a multidrug-resistant *P. vivax* strain, treatment with artesunate and PS was prescribed, followed by primaquine (30 mg/d) for 15 days. He recovered in 24 hours, and parasite control (blood smear) at days 7, 14, and 28 were negative, as was blood PCR for malaria at day 28. The patient is still asymptomatic 9 months after this episode.

**Case 2**

A 49-year-old man had spent 2 weeks in a hunting trip to Cameroon and had taken A/P for prophylaxis, according to recommended standards. The patient reported having been in good health until 4.5 months after his return when he started with fever, headache, and malaise. His medical history only included prostate benign hypertrophy, fatty liver, and hyperuricemia. In another hospital, he was diagnosed as having acute prostatitis and was treated with antibiotics (levofloxacin plus tobramycin) without clinical improvement. Seven days after his admission, he was transferred to our hospital. On arrival he was febrile (temperature 38°C), his blood pressure 150/65 mm Hg, his heart rate 95 beats per minute, and his respiratory rate 16 breaths per minute. Abdominal examination showed a spleen tip. Laboratory data revealed a white blood cell count at 4,300/mL (normal differential), a hemoglobin level at 12.3 g/dL, and a platelet count at 85,000/mL. Liver function tests were abnormal, with alanine aminotransferase (ALT) 67 U/L, aspartate aminotransferase (ALT) 67 U/L, aspartate aminotransferase (AST) 81 U/L, gamma-glutamyl transpeptidase (GGT) 628 U/L, and lactic dehydrogenase (LDH) 451 U/L. Urine and electrolytes were normal, blood culture and urine culture were sterile. A chest x-ray was performed, with no abnormal findings. Thick and thin blood films showed malaria parasites due to *P. ovale*, with a parasite density of 0.5%, which was confirmed by seminested multiplex PCR assay. It was not possible to recover CYT *b* DNA from the blood sample. Treatment was started with chloroquine 25 mg base/kg (1,300 mg base) over 72 hours. Testing of glucose-6-phosphate dehydrogenase prior to prescription of primaquine as radical cure for *P. ovale* infection showed a nearly total deficiency of this enzyme, which contraindicated the use of this drug. Blood parasite control at days 7, 14, and 28 was negative, as was blood PCR at day 28. Three months after treatment, the patient is still asymptomatic.

**Discussion**

The use of blood-stage schizocides does not prevent relapses, and it can mask symptoms of late malaria, normally months later, as it happened in case 2 in whom a prostate infection instead of malaria was suspected.

The number of available agents for liver-stage (causal) prophylaxis is limited. Primaquine and tafenoquine are the only current drugs effective as tissue schizocides that will prevent relapses, but data on their efficacy among travelers are limited. The main disadvantage of those drugs is the risk of hemolytic anemia in persons with glucose-6-phosphate dehydrogenase deficiency. In case 2, nearly total deficiency of this enzyme contraindicated the use of primaquine, thus leaving no treatment option for radical cure.

Atovaquone is a hydroxynaphthoquinone that inhibits mitochondrial electron transport, reducing pyrimidine synthesis and causing collapse of the membrane electrochemical potential. Proguanil inhibits dihydrofolate reductase (via its metabolite cycloguanil) and enhances synergistically the effect of atovaquone in asexual blood stages. Neither of them is highly effective when used alone but the combination kills blood stages of *P. falciparum* and *P. vivax*, showing a high efficacy on the treatment of noncomplicated malaria. Four randomized, placebo-controlled trials reported that a fixed-dose combination of atovaquone (250 mg) and proguanil (100 mg) was 97% to 100% effective in prevention of malaria caused by *P. falciparum* on lifelong residents (adults and children over 11 kg) of malaria-endemic countries in Africa, who may have some immunity to malaria (premunition). In addition, it has demonstrated causal prophylactic activity on tissue forms of *P. falciparum*. For this reason, A/P prophylaxis can be discontinued shortly (1 week) after departure from an area of risk.

Ling and colleagues conducted the only randomized placebo-controlled trial till date that has evaluated the efficacy of A/P for the prevention of *P. vivax* malaria in individuals without prior malaria exposure. The study was carried out in 297 transmigrants from Java to Papua (Indonesia) and showed that the protective efficacy of A/P was high (96%) for malaria caused by *P. falciparum* and moderate (84%) for that caused by *P. vivax*, with a wide confidence interval (44%–95%). But only one case report of malaria caused by *P. vivax* in a Western traveler taking A/P for prophylaxis has been described...
and sequence analysis of cytochrome b gene found no mutations for resistance.  

Failure of A/P could be questioned in case 1 as the patient had a prior malaria episode treated with mefloquine and PS after travel to East Africa and the Indian subcontinent, and \textit{P. vivax} could have been acquired there and not during his travel to Papua New Guinea. This is unlikely because the time elapsed between the first episode and the second one is 34 months and because he had traveled to a highly \textit{P. vivax}–endemic country 2.5 months before.

A case of malaria caused by \textit{P. ovale} of 511 Western travelers to Africa taking A/P has been reported, with symptoms initiating 28 days after completing prophylaxis.  

This patient was taking part in a randomized, double-blind prophylaxis trial comparing Malarone with chloroquine–proguanil, but the study was designed to evaluate tolerability and not efficacy as the primary end point. Another case of malaria caused by \textit{P. ovale} despite A/P was observed in an open case–control study of Danish travelers that evaluated the risk of malaria infection at common destinations and the efficacy of different drugs used for prophylaxis. The patient presented symptoms several months after return from Ghana.  

Prophylaxis failure with A/P has also been described in patients other than Western travelers: Lacy and colleagues reported three cases of malaria (two \textit{P. vivax} infections and one mixed \textit{P. vivax} and \textit{P. falciparum} infection) in Indonesian transmigrants despite A/P.

Cases of prophylaxis failure without genetical resistance, like case 1, suggest that factors other than cytochrome b mutations may be implicated in the limited efficacy against establishment and survival of hypnozoites of \textit{P. vivax}. At the molecular level, atovaquone acts on the mitochondrial electron transport at the level of the cytochrome bc1 complex (complex III). Certain single-point mutations on cytochrome b (position 268) region of mitochondrial DNA have been associated with atovaquone resistance. These mutations imply lack of susceptibility of the blood stages to A/P. To date, very few cases of genetically confirmed resistance to A/P have been reported, all associated with treatment failure. Moreover, to the present, there are no known drug resistances of \textit{P. ovale}.

As a conclusion, we can say that tertian malaria caused by \textit{P. vivax} and \textit{P. ovale} is possible in Western travelers despite A/P prophylaxis. Symptoms start 5 to 18 weeks after return. Though data are limited, probably this might not be due to drug resistance but limited causal activity against these species. Additional studies are needed to determine the activity of A/P against hypnozoites of \textit{P. vivax} and \textit{P. ovale}.

**Declaration of Interests**

The authors state that they have no conflicts of interest.

**References**