FAILURE OF ATOV AQ UONE/PRO GUAN I L TO PREVENT 
Plasmodium ovale malaria in traveler returning 
from Cameroon

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Summary
We report a case of a patient returning from Cameroon who developed Plasmodium ovale malaria, despite atovaquone/proguanil (AP, Malarone) prophylaxis, which is widely used for the prevention of chloroquine-resistant malaria. AP is indeed active only on schizont blood forms of P. ovale but not against liver-stage hypnozoites and does not realize effective prophylaxis against delayed onset of P. ovale malaria. Hence, this case illustrates the risk of failure with Malarone for the prophylaxis of P. ovale infection for travelers in endemic regions. Travelers returned from risk areas with symptoms suggestive of malaria, should not have the diagnosis of P. ovale (or P. vivax) infection discounted, despite a history of compliance with a standard chemoprophylactic regimen.

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Introduction
Plasmodium ovale infection is less commonly seen in travelers than P. falciparum or P. vivax and is found almost exclusively in West Africa. Chloroquine is the drug recommended either for chemoprophylaxis or treatment of P. ovale malaria, and up to now no chloroquine resistance has been described.

The combination of atovaquone and proguanil (AP), marketed under the trade name of Malarone, is a recently developed drug combination with blood-stage and liver-stage activity against P. falciparum and has proved to be effective both for treatment and prophylaxis of
chloroquine-resistant malaria in both adult and pediatric populations. Of because of its favorable safety profile, the requirement for just 7 days use after return and its high protective efficacy against chloroquine-resistant \( P. falciparum \), AP is now very commonly prescribed to travelers to chloroquine-resistant malaria-endemic areas. We report a patient returning from Cameroon with documented \( P. ovale \) malaria despite AP prophylaxis.

**Case report**

A 69-year-old male, who had returned 8 weeks earlier from Cameroon, was admitted to the infectious disease department because of fever and headaches lasting for 5 days. The patient reported to have stayed in a forest area in the middle of Cameroon, near Yaounde, and to have taken AP prophylaxis according to recommended standards and with a strict daily adherence, including 7 days use after returning to France. He also used personal protective measures against mosquitoes using daily DEET on his body, on his clothes and also on mosquito netting around the bed. Physical examination was normal except fever of 39 °C. Laboratory analysis revealed a white blood cell count of 5400/mL, with 75% polymorphonuclear cells. The hemoglobin level was 14.2 g/dL and the platelet count was low at 79,000/mL. Thick and thin blood smears showed malaria parasites, identified as \( P. ovale \). He was treated with therapeutic doses of hydroxychloroquine according to WHO guidelines (i.e., 25 mg/kg over 3 days) and he quickly improved.

**Discussion**

\( P. ovale \), unlike \( P. falciparum \), is not associated with severe malaria but may, like \( P. vivax \) cause recurrent episodes of malaria, as the parasite starts a new blood cycle from latent intra-hepatocytic forms (hypnozoites) which may persist for months after a first episode of malaria. Schwartz et al. reported that, from more than 3000 cases of malaria among returning travelers, 1.7% to 3% are due to \( P. ovale \) despite the use of effective prophylaxis in 72% to 80%.

AP is only active on schizont blood forms of \( P. ovale \) and does not appear to have activity against the latent liver-stage hypnozoites. AP is, however, active against both \( P. falciparum \) liver-stage merozoites and blood-stage parasites; \( P. falciparum \) is not a relapsing malaria and there is no latent hepatic hypnozoite in its life cycle. Thus, AP acts only as a suppressive prophylactic agent against \( P. ovale \), and after dosing is discontinued and the drug eliminated, a delayed onset of malaria can occur, caused by hypnozoites.

Only three other cases have been reported of \( P. ovale \) infection in travelers using AP prophylaxis: one occurring several months after a traveler returned from Ghana, the other occurring 4.5 months after returning from Cameroon, and one case 28 days after completing prophylaxis with AP. The course of these three previous cases as well as the current one is consistent with this process. Similarly, occurrences \( P. vivax \) infection despite AP prophylaxis have also been reported.

In this context, the hypothesis that \( P. ovale \) demonstrated resistance to AP, previously described only with \( P. falciparum \), is very unlikely. In conclusion, AP used for chemoprophylaxis in chloroquine-resistant areas in West Africa cannot reliably prevent \( P. ovale \) or \( P. vivax \) infection or clinical disease, and travelers are potentially at risk of delayed onset \( P. ovale \) malaria against which no fully effective prophylaxis is available. Thus, travelers, who can develop malaria caused by \( P. ovale \), could require additional treatment with primaquine, an antimalarial agent with activity against liver-stage \( P. ovale \). Primaquine is contraindicated in pregnancy and individuals with low glucose-6-phosphate dehydrogenase levels. Thus, primaquine therapy can be utilized either to eradicate presumptive hypnozoites, both for \( P. ovale \) and \( P. vivax \), a practice known as “terminal prophylaxis”, in order to prevent a delayed primary attack, which can occur up to 4 years after the exposure, or for a radical cure, in association with chloroquine, in documented relapsing malaria, which remains, however, a rare eventuality for \( P. ovale \) (<1%) but up to 50% for \( P. vivax \).

Prophylaxis prescribers and those advising and treating travelers should remember that chemoprophylactic regimens are designed for use against \( P. falciparum \). Travelers returned from risk areas with symptoms suggestive of malaria should not have the diagnosis of \( P. ovale \) (or \( P. vivax \)) infection discounted, despite a history of compliance with a standard chemoprophylactic regimen.

**References**