ATOVAQUONE-PROGUANIL: REPORT FROM THE CDC EXPERT MEETING ON MALARIA CHEMOPROPHYLAXIS (II)

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Abstract. The fixed dose combination of atovaquone and proguanil hydrochloride, marketed under the trade name Malarone™, is the most recently approved agent in North America for the prevention and treatment of chloroquine- and multi-drug resistant Plasmodium falciparum malaria. In both adult and pediatric populations, atovaquone-proguanil demonstrates consistently high protective efficacy against P. falciparum, and in treatment trials, cure rates exceed 93%. Only a handful of genetically confirmed treatment failures have been reported to date. Atovaquone-proguanil has an excellent safety profile during both prophylaxis and treatment courses, with severe adverse events rarely reported. This topical review will examine the evidence behind the current indications for use of atovaquone-proguanil, and will summarize the current body of literature surrounding safety and tolerability.

SUMMARY

Indications. Prophylaxis of Plasmodium falciparum malaria in adults and children weighing ≥ 11 kg traveling to or residing in areas of chloroquine and multidrug resistance (AI*). Current evidence supports the use of atovaquone/proguanil for prophylaxis of Plasmodium vivax malaria (AI), although it is not currently FDA-approved for this indication.

Treatment of uncomplicated P. falciparum malaria in adults and children weighing ≥ 5 kg (AI).

Dosing. Adult. Adult tablets contain 250 mg atovaquone and 100 mg proguanil.

Prophylaxis: 1 adult tablet once daily, started 1–2 days before travel, taken during travel, and for 7 days after departure from malarious area.

Treatment: Four adult tablets taken once daily for 3 days (total dose 12 tablets) Malarone tablets should be taken with food or a fatty drink.

Pediatric. Pediatric tablets contain 62.5 mg atovaquone and 25 mg proguanil.

Prophylaxis:

Weight-based dose: 5–8 kg—0.5 tablet once daily
> 8–10 kg—0.75 tablet once daily
> 10–20 kg—one tablet once daily
> 20–30 kg—two tablets once daily
> 30–40 kg—three tablets once daily
> 40 kg—one adult tablet once daily

Of note, prophylactic dosing for children weighing < 11 kg constitutes off-label use in the United States.

Treatment: As with prophylaxis, treatment is weight-based and 3 days in duration.

Weight-based dose: 5–8 kg—two pediatric tablets once daily
> 8–10 kg—three pediatric tablets once daily
> 10–20 kg—one adult tablet once daily
> 20–30 kg—two adult tablets once daily
> 30–40 kg—three adult tablets once daily
> > 30–40 kg—three adult tablets once daily
> > 40 kg—four adult tablets once daily (adult dose)

Efficacy. Prophylaxis: Randomized, placebo-controlled and comparator trials show 96–100% protective efficacy of AP against P. falciparum malaria at standard doses in adult and pediatric populations.

Treatment: Randomized comparator clinical trials indicate cure rates of uncomplicated P. falciparum malaria of 87–100%, with eight of nine trials showing radical cure rates of > 93%.

Adverse Drug Reactions. Most common mild/moderate ADRs+: Nausea, vomiting, abdominal pain, headache, diarrhea. Five percent to 10% of those receiving treatment doses develop asymptomatic elevation of hepatic transaminases. Severe+: Rate of discontinuation of prophylaxis in RCTs is 0–1.8%. There were no significant differences in moderate/severe ADRs between AP and comparators in prophylaxis or treatment trials. Treatment-limiting severe ADRs occur in < 1% of patients.

Contraindications. AP is contraindicated in those who have known hypersensitivity to either atovaquone or proguanil. One case of anaphylaxis has been documented in a patient receiving AP for treatment of uncomplicated falciparum malaria. Atovaquone-proguanil is contraindicated in individuals with severe renal impairment (CrCl < 30 mL/min).

Precautions. Atovaquone–proguanil is not indicated for the treatment of complicated malaria. Parasite recurrence occurs commonly when AP is used as monotherapy for P. vivax malaria. Absorption of atovaquone may be impaired in patients with vomiting or diarrhea, although controlled treatment trials indicate high cure rates (98%) if patients with these symptoms are concurrently administered antiemetics.

Drug Interactions. Concurrent use of tetracycline, metoclopramide, rifampin, or rifabutin and atovaquone-proguanil is not recommended because of reduction in plasma concentration of atovaquone. Atovaquone increases the AUC of zidovudine and etoposide; thus, caution should be exercised during concomitant administration.

Use During Pregnancy. Pregnancy category C§. An insufficient number of trials have been performed to clearly show safety. One small randomized, open-label treatment trial did
not show a difference in birth weight, duration of gestation, congenital anomalies, or growth and developmental parameters at 1 year between the atovaquone-proguanil arm and quinine arm. Atovaquone-proguanil is currently not recommended for use during pregnancy.

**Use During Breastfeeding.** Proguanil is excreted into breast milk in small quantities. It is unknown whether atovaquone is excreted into human breast milk. Currently, AP is not recommended for women breastfeeding infants weighing < 5 kg.

**Use in Children.** Randomized controlled trials indicate that atovaquone–proguanil is safe and efficacious as a chemoprophylactic agent for *P. falciparum* malaria in children weighing ≥ 11 kg. Treatment efficacy, safety, and pharmacokinetic data in children 5–11 kg have been extrapolated to recommend prophylaxis doses in children 5–11 kg (off-label use). The safety and efficacy of AP for the treatment of falciparum malaria have been established for children weighing ≥ 5 kg.

* USPHS Recommendation Grading System.†
† Reported in at least two studies at > 2% frequency.
‡ Severe ADRs include those that interfere with activities of daily living, necessitate medical attention, or are listed under mild-moderate ADRs but are severe in intensity.
§ FDA pregnancy category C: either studies in animals have revealed adverse effects on the fetus and there are no controlled studies in women or studies in women and animals are not available. Drugs should only be given if the potential benefit justifies the potential risk to the fetus.

**INTRODUCTION**

Atovaquone-proguanil (AP) is a fixed dose combination of the antimalarial drugs atovaquone and proguanil hydrochloride and is marketed in North America under the trade name Malarone (GlaxoSmithKline, Inc.). The adult tablet combination consists of 250 mg atovaquone and 100 mg proguanil hydrochloride, whereas the pediatric formulation contains 62.5 mg atovaquone and 25 mg proguanil per tablet. Malarone is the most recently approved agent used to prevent and treat chloroquine- and multidrug-resistant *Plasmodium falciparum* malaria in North America. Randomized controlled trials in adults and pediatric populations show high protective efficacy against *P. falciparum*, and in randomized treatment trials, cure rates are consistently > 90%. To date, only a small number of genetically confirmed treatment failures have been reported.

The clinical efficacy of AP is complemented by its safety and tolerability, which have been examined in > 3,000 children and adults during prophylaxis and treatment trials. Severe adverse drug reactions are rare. Atovaquone’s mechanism of action is through inhibition of parasite electron transport at the level of the cytochrome bc1 complex. Whereas the proguanil metabolite cycloguanil acts by inhibiting parasite dihydrofolate reductase (DHFR), it is the parent drug proguanil that seems to act synergistically with atovaquone. The combination AP has synergistic activity against blood stages and causal activity against the primary schizonts of the parasite and thus can be discontinued 7 days after departing a malarious region. The short duration of prophylaxis after departure from a malarious area may improve adherence.

**RECOMMENDED USES AND DOSING OF AP**

AP is used for the chemoprophylaxis of malaria in adults and children traveling to or residing in areas of chloroquine or multidrug resistance (AI; note: labeled indication is for the prevention of *P. falciparum* malaria only). It is also indicated for treatment of uncomplicated *falciparum* malaria.3–5

**Prophylaxis.** AP used for antimalarial chemoprophylaxis requires 1 adult tablet (fixed-dose combination of atovaquone 250 mg + proguanil hydrochloride 100 mg) daily beginning 1–2 days before exposure, throughout exposure, and continuing for 7 days after departure from the malaria risk area.3–5 A pediatric formulation exists, and the prophylactic dosing regimen for children is weight-based as follows: 5–8 kg, ½ pediatric tablet (fixed dose combination of atovaquone 62.5 mg + proguanil hydrochloride 25 mg); > 8–10 kg, ¾ pediatric tablet; > 10–20 kg, one pediatric tablet; > 20–30 kg, two pediatric tablets; > 30–40 kg, three pediatric tablets; > 40 kg, one adult tablet. As with the adult formulation, pediatric tablets should be taken once daily beginning 1–2 days before exposure, throughout exposure, and for 7 days after exposure. AP is not labeled for use as a prophylactic agent in children weighing < 11 kg.6 However, randomized clinical trials have shown AP to be safe and efficacious in the treatment of falciparum malaria in children down to 5 kg. In addition, pharmacokinetic data support this recommendation (see section below on Children). Thus, the Centers for Disease Control (CDC) now recommends AP as an option for prophylaxis in children weighing ≥ 5 kg (B3).

All prophylactic studies to date have assessed the use of AP before exposure. It is unknown whether AP will function as a causal agent when started after exposure to malaria; therefore, individuals who switch from a blood schizonticide agent such as mefloquine (MQ) or doxycycline to AP during exposure should take AP for 4 weeks after the drug change or 1 week after returning from the malaria-endemic area, whichever is longer, but not beyond 4 weeks after return.3–7

**Treatment.** Standard recommended therapy for adults with uncomplicated *P. falciparum* malaria is AP, four adult tablets once daily for 3 days. It is recommended that tablets be consumed with food or a fatty drink. In children weighing ≥ 5 kg, daily treatment dose is weight-based as follows: 5–8 kg, two pediatric tablets; > 8–10 kg, three pediatric tablets; > 10–20 kg, one adult tablet; > 20–30 kg, two adult tablets; > 30–40 kg, three adult tablets; > 40 kg, four adult tablets. As with adults, duration of treatment in children is 3 days.3–5

**EFFICACY AND EFFECTIVENESS**

**Prophylaxis.** In randomized controlled trials, daily AP at recommended dosing was highly efficacious in preventing *P. falciparum* malaria in both non-immune and semi-immune adults and children. Four published trials have examined the protective efficacy of AP in 534 semi-immune adults and children living in areas of *P. falciparum* endemicity (Table 1).3–12 Development of parasitemia was the primary endpoint in each study, and protective efficacy of AP against *P. falciparum* infection was 97–100% (95% CI, 77–100%). Two of the trials were randomized, double-blind, placebo-
controlled, and evaluated the protective efficacy and safety profile of AP in semi-immune adults. In the first study, Kenyan adults were administered a standard treatment course of AP to eradicate baseline parasitemia. Participants were randomized to one of three arms: placebo (N = 54), standard AP (one adult tablet, N = 54), or high-dose AP (two adult tablets, N = 54) daily for 10 weeks. No participant in either AP arm developed parasitemia, whereas 52% in the placebo arm developed parasitemia during the period of prophylaxis. In a similar trial, 274 Zambian adults were randomized to standard AP prophylaxis (N = 136) or placebo (N = 138) for 10 weeks after curative therapy with 3 days AP. Parasitemia was observed in 2 participants from the AP group and in 41 participants from the placebo arm. In one of the cases of prophylaxis failure, serum concentrations of proguanil and cycloguanil were extremely low in the face of normal atovaquone levels, suggesting that AP/cycloguanil synergy is important for prophylactic and treatment efficacy.

Two of these trials were randomized, double-blind, placebo-controlled trials that evaluated the protective efficacy against *P. falciparum* and safety profile of AP in semi-immune Gabonese children. Lell and others enrolled 320 schoolchildren (4–16 years of age) from a hyperendemic area for *P. falciparum* in one trial, and after a 3-day treatment course with AP, randomized them to either placebo (N = 140) or AP (N = 125) daily prophylaxis. During the 12-week course of chemosuppression, no cases of parasitemia were detected in the AP arm, whereas 25% (18%) in the placebo arm developed parasitemia. In the second trial, 330 Gabonese schoolchildren (4–16 years of age) were randomized to either placebo (N = 165) or AP prophylaxis (N = 165) for 12 weeks after a 3-day curative course with artesunate. One child from the AP group developed *P. falciparum* parasitemia during the chemosuppression phase compared with 31% (22%) from the placebo group.

The protective efficacy of AP for prevention of *P. falciparum* malaria in non-immune adults and children has been examined in five clinical trials, four of which were randomized, and three were blinded. Collectively, the protective efficacy of AP (evaluable in 1,361 non-immune individuals, of whom 126 were children under the age of 12 years) was 96–100% (95% CI, 48–100%). However, the determination of protective efficacy in some of these trials was limited by lack of a placebo control. These studies, which included comparator arms, were inadequately powered to show either the superiority or equivalence of one arm compared with the other. In four trials, tolerability/adverse events were the primary outcome, and efficacy was the secondary outcome, and in the other trial, the primary endpoint was *P. vivax* parasitemia, with *P. falciparum* parasitemia a secondary endpoint.

An open-label safety and efficacy trial of AP for the prophylaxis of *P. falciparum* malaria was conducted in 175 non-immune adults in South Africa. Participants were volunteers who would be living in or traveling to a malaria-endemic zone for up to 10 weeks. Participants received standard dosing (one adult tablet daily) of AP throughout the study period. Of the 113 evaluable subjects, 1 developed parasitemia during chemoprophylaxis but was excluded from the efficacy analysis because of known non-adherence. Another three individuals withdrew because of adverse drug reactions (ADRs; two with headache, one with nausea + dizziness); thus, the protective efficacy was determined to be 97% (95% CI, 92–99%). A lack of comparator in this trial limits the interpretability of these efficacy data.

Two more recent, randomized, double-blind comparator trials also suggest that protective efficacy of AP against *P. falciparum* malaria is high. In one equivalence trial, non-immune travelers to Africa or South America were randomized to either daily AP + placebo (N = 540) or chloroquine-proguanil (CP) + placebo (N = 543). Serum samples were obtained 28 days after travel for measurement of anti-
circumsporozoite protein antibodies, which were used as a surrogate marker of malaria exposure. Of 507 evaluable participants in the CP group, 3 developed P. falciparum malaria, and of 501 evaluable subjects in the AP arm, 1 developed P. ovale malaria.14 Thus, the minimum efficacy for prevention of P. falciparum malaria in the AP arm was estimated to be 100% (95% CI, 95–100%) and in the CP arm, it was 70% (95% CI, 35–93%).14 A second, multicenter trial conducted at 15 centers on three continents compared the safety and efficacy of AP to MQ for prophylaxis of P. falciparum malaria in non-immune travelers (79% to Africa) over the age of 3 years.15 Travelers were randomized to receive standard daily prophylactic dosing of AP (N = 508) or weekly MQ (N = 505). Of 486 evaluable participants in the AP arm and 477 in the MQ arm, none developed parasitemia during the study period.15 Thus, minimum protective efficacy for the prevention of P. falciparum malaria was estimated to be 100% (95% CI, 90–100%) for both groups.15 It is important to note, however, that these studies lacked a placebo group, and so antimalarial efficacy could not be adequately determined. Both superiority and equivalence trials comparing two efficacious drugs require a much greater number of participants than the level of enrollment achieved in these two trials.18

One randomized, multicenter, open-label trial has compared the safety and protective efficacy of AP to CP for prevention of P. falciparum malaria in non-immune pediatric travelers (weight, 11–50 kg).17 In this trial, 232 children (2–17 years of age) were randomized to either AP (N = 117) or CP (N = 115) prophylaxis before planned travel of ≤28 days. Participants were followed to 60 days after travel. No subjects were diagnosed with malaria during the study period; thus, protective efficacy was deemed to be 100% for each drug, although again, the lack of a placebo group limits the interpretation of efficacy.

Only one randomized, double-blind, placebo-controlled trial has evaluated the protective efficacy of AP against P. vivax.16 Ling and others16 enrolled 297 adults who had migrated from non-endemic Java to endemic Papua within 26 months of the study period. Subjects received one adult tablet of AP daily (N = 148) or placebo (N = 149) for 20 weeks.16 Parasitemia occurred in 37 subjects in the placebo arm (14 cases of P. vivax, 21 of P. falciparum, 2 cases of vivax-falciparum co-infection), and in 3 participants in the AP arm (2 cases of P. vivax, 1 case of vivax-falciparum co-infection). The protective efficacy of AP was 84% (95% CI, 45–95%) for P. vivax and 96% (95% CI, 71–99%) for P. falciparum.16 Because AP does not seem to eradicate P. vivax hypnozoites,19 and may not prevent the establishment of hypnozoites,20 it is suggested that travelers to areas where the transmission rates of P. vivax are high should receive consideration for presumptive anti-relapse therapy (PART) with primaquine.

Prophylaxis failures of AP are rare among travelers when adherence is high. In the United States in 2004, there were four reported cases of AP prophylaxis failure among adherent travelers.21 Two infections were caused by P. vivax in travelers to Burma (Myanmar) and Brazil and two by P. falciparum in travelers to Mozambique and Nigeria.21 Using the number of cases reported through the National Malaria Surveillance System (NMSS) and prescription data provided by GlaxoSmithKline (GSK), the CDC has estimated the prophylaxis failure rate among those who are adherent to AP to be 2.01 cases per 100,000 prescriptions, with a rate ratio of 0.36 (95% CI, 0.12, 0.50).21 Assuming a 3-week travel period and that each prescription represents and individual traveler, this translates into a prophylaxis failure rate for AP of 0.0007 per 100 person-weeks.

Treatment. AP has shown efficacy for the treatment of uncomplicated P. falciparum acquired in areas with chloroquine- and multidrug-resistant parasites in adults and children, with cure rates of 87–100% (95% CI, 80–100%) in randomized, comparator trials (Table 2).22–30 In eight of nine trials, the cure rate for P. falciparum was ≥94%, with a 28-day cure rate being the primary efficacy endpoint in seven of nine trials.22–26,29,30

Three randomized trials have evaluated the curative efficacy of AP for the management of uncomplicated P. falciparum malaria in semi-immune adults.22–24 Radloff and others22 randomly assigned 142 Gabonese adults with P. falciparum malaria to a 3-day treatment course with AP (N = 71) or amodiaquine (AQ; N = 71). Patients were followed for 28 days or until recrudescence. Of 126 participants followed for 28 days, 62 (87%) in the AP arm and 51 (72%) in the AQ arm were cured (P = 0.022). One patient from the AP group had recrudescent parasitemia at day 28, and 12 patients from the AQ group had recrudescence at day 14, 21, or 28.22 It is possible that some “recrudescence” represented re-infection because molecular analyses to distinguish the two was not performed. In a second randomized, comparative trial, semi-immune Brazilian adult men with uncomplicated malaria (P. vivax, P. falciparum, or mixed) were treated with either 3 days of AP (N = 77) or 7 days of quinine/tetracycline (N = 77) and followed for a total of 28 days.23 Recrudescence occurred in one subject from the AP arm and in no subjects from the quinine/tetracycline arm, yielding cure rates of 98.7% and 100%, respectively (P = not significant).23 Cure rates for infection with P. falciparum alone were similar at 98.6% in the AP arm versus 100% in the quinine/tetracycline arm.23 A third randomized, comparator trial was performed in 163 semi-immune Zambian adults.24 Subjects with acute uncomplicated P. falciparum malaria were randomized to 3-day treatment with AP (N = 82) or single-dose sulfadoxine-pyrimethamine (SP, N = 81) and followed for 28 days.24 Cure rates for AP and SP were 100% and 98.8%, respectively (P = not significant).24

Three additional randomized, open-label comparator trials were performed in Southeast Asia and included participants who may have had some degree of partial immunity to P. falciparum malaria. Bustos and others25 randomized 110 Filipino patients (12–65 years of age) with acute, uncomplicated falciparum malaria to treatment with AP (N = 55), CQ (N = 23), or CQ + SP (N = 32) and followed them for 28 days. Cure rates for the three arms were as follows: 100% in the AP group, 30.4% in the CQ group (P < 0.001), and 87.5% in the CQ + SP group (P < 0.005).23 In a second trial, 182 Thai patients with acute uncomplicated P. falciparum malaria were randomized to 3-day treatment with AP (N = 91) or two doses of MQ (N = 91).26 All 79 evaluable patients in the AP arm were cured at 28-day follow-up versus 68/79 (86%) of evaluable patients in the MQ arm (P < 0.002).26 Another randomized, open-label comparator trial was conducted in Thailand in a region of low and unstable transmission of P. vivax and P. falciparum on the western border.28 A total of 1,596 adults and children (weight > 10 kg) with uncomplicated
P. falciparum malaria were randomly allocated to treatment with AP (N = 530), artesunate-mefloquine (N = 533), or artesunate AP (AAP; N = 533) and followed for 42 days. By day 42 of follow-up, polymerase chain reaction (PCR)-confirmed recrudescence had occurred in 15/530 in the AP arm, 13/533 in the artesunate-mefloquine arm, and 5/533 in the AAP arm, yielding cure rates of 97.2%, 97.6%, and 99.7%, respectively. 28

Only one randomized, comparator trial has evaluated the treatment efficacy of AP for P. falciparum in non-immune adults. 27 In this multicenter, open-label study, 48 non-immune adults with imported, uncomplicated P. falciparum malaria were randomized to standard treatment with AP (N = 25) or halofantrine (HF; N = 23), and followed for 35 days after hospital discharge. 27 Nearly all participants had acquired their malaria while traveling in sub-Saharan Africa. All evaluable patients (21 in the AP arm and 20 in the HF arm) were successfully treated. 27

Finally, two randomized, open-label comparative trials have evaluated treatment efficacy of AP for P. falciparum malaria in children. 29,30 Anabwani and others 29 randomized 168 Kenyan children (3–12 years of age, weight > 10 kg) with acute uncomplicated P. falciparum malaria to weight-based treatment with either AP (N = 84) or HF (N = 84) and followed them for 28 days. 29 Both interventions resulted in high cure rates (94% in the AP arm and 90% in the HF arm) that did not differ significantly (P = 0.59). Patients who failed therapy were re-treated with the drug to which they were randomized. All four patients re-treated with HF were cured, and two of three patients retreated with AP were cured. 29 On patient failed re-treatment with AP and was subsequently cured with HF. 29 In a second trial, 200 Gabonese children (3–43 months of age; weight, 5–11 kg) with uncomplicated P. falciparum malaria were randomized to receive treatment with AP (20/8 mg/kg/d, N = 100) or amodiaquine (AQ; 10 mg/kg/d, N = 100) for 3 days and followed for 28 days. 30 The cure rate in the AP arm was 95% (87/92 evaluable patients) versus 53% (41/78 evaluable patients) in the AQ arm (P < 0.0001). 30 Loss to follow-up was significantly higher in the AQ group (11 versus 3 patients, P = 0.024). 30

The curative efficacy of AP has been evaluated to a lesser degree in other species of Plasmodium. Treatment doses of AP were effective in initially eradicating blood stages of P. vivax in 19/19 patients treated in Thailand. 31 However, 13/19 patients (68%) had recurrent parasitemia, possibly reflecting recrudescence or relapse, between 19 and 28 days of follow-up. 31 In a subsequent open-label treatment trial, 48 patients with confirmed vivax malaria were treated with a standard, 3-day course of AP, followed by 30-mg base of daily primaquine for 14 days. 19 Of 44 patients who completed the 14-day course of primaquine, only 2 developed recurrent para-

<table>
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<tr>
<th>Country (population)</th>
<th>Study type</th>
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<tr>
<td>Gabon (semi-immune, aged 15–65 years) 22</td>
<td>Randomized, open-label, comparator = AQ (N = 71)</td>
<td>71/four adult tabs daily</td>
<td>3 days</td>
<td>87% (80–85%) AP vs. 72% (61–82%) AQ</td>
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<td>Brazil (semi-immune men) 23</td>
<td>Randomized, open-label, comparator = quinine + tetracycline (N = 77)</td>
<td>77/four adult tabs daily</td>
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<td>98.7% (92–99%) AP vs. 100% (95–100%) O+T</td>
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<td>Zambia (semi-immune, aged 14–54) 24</td>
<td>Randomized, open-label, comparator = SP (N = 80)</td>
<td>80/four adult tabs daily</td>
<td>3 days</td>
<td>100% AP vs. 98.8% SP</td>
</tr>
<tr>
<td>Philippines (children age &gt; 12 years + adults) 25</td>
<td>Randomized, open-label, comparators: CQ (N = 23) and CQ+SP (N = 32)</td>
<td>54/30–40 kg, three adult tabs daily &gt; 40 kg, four adult tabs daily</td>
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<td>100% AP vs. 99.4% CQ vs. 87.5% CQ+SP</td>
</tr>
<tr>
<td>Thailand (adults) 26</td>
<td>Randomized, open-label, comparator = MQ (N = 79)</td>
<td>79/four adult tabs daily</td>
<td>3 days</td>
<td>100% AP vs. 86% MQ</td>
</tr>
<tr>
<td>Thailand (aged 2–70 years, weight &gt; 10 kg) 28</td>
<td>Randomized, open-label, comparators = AAP (N = 526) and A+MQ (N = 532)</td>
<td>525/11–20 kg, one adult tab daily 21–30 kg, two adult tabs daily 31–40 kg, three adult tabs daily &gt; 40 kg, four adult tabs daily</td>
<td>3 days</td>
<td>97.2% (95.4–98.4%) AP vs. 97.6% (95.9–98.8%) A+MQ vs. 99.1% (97.9–99.7%) AAP</td>
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<tr>
<td>Multicenter (non-immune adult travelers, majority to sub-Saharan Africa) 27</td>
<td>Randomized, open-label, comparator = HF (N = 20)</td>
<td>21/four adult tabs daily</td>
<td>3 days</td>
<td>100% (84–100%) AP vs. 100% (83–100%) HF</td>
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<td>Kenya (children aged 3–12 years) 29</td>
<td>Randomized, open-label, comparator = HF (N = 83)</td>
<td>81/11–20 kg, one adult tab daily 21–30 kg, two adult tabs daily 31–40 kg, three adult tabs daily</td>
<td>3 days</td>
<td>93.8% AP vs. 90.4% HF</td>
</tr>
<tr>
<td>Gabon (children aged 3–43 months, weight 5–11 kg) 30</td>
<td>Randomized, open-label, comparator = AQ (N = 78)</td>
<td>92/5–9 kg, two ped tabs daily 9–11 kg, three ped tabs daily</td>
<td>3 days</td>
<td>95% AP vs. 53% AQ</td>
</tr>
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* Number evaluable for cure.
asitemia at day 56 (cure rate, 95.5%). A similar small treatment trial of 3-day AP followed by 14-day primaquine showed a 28-day cure rate of 100% for *P. vivax* in 16 Indonesian participants. Finally, a case series has reported efficacy of AP for the treatment of *P. ovale* and *P. malariae* malaria; however, the small sample size (N = 7) limits interpretation of these findings.

Outside of treatment trials, reports of AP treatment failure are rare. As of July 2005, there have been 12 published cases of AP failure for the treatment of *P. falciparum* malaria, only 7 of which have had isolates with genetically confirmed markers of resistance, notably mutations in the cytochrome *b* gene (Table 3). A small number of reported failures have been reported with parasites possessing wild-type cytochrome *b*; however, to date, these cases have been less definitive, for example, not all of these cases ensured directly observed therapy, adequate drug levels, and none of these isolates has been cultured to confirm resistance in vitro. Alternative molecular mechanisms of resistance other than mutations in cytochrome *b* have yet to be defined. Seven cases of AP treatment failure have been documented in non-immune travelers, with the remaining five occurring in semi-immune individuals. All published failures have occurred in patients whose malaria was acquired in Africa (Table 3).

**PHARMACOKINETICS AND PHARMACODYNAMICS**

**Pharmacokinetics.** Pharmacokinetic studies in healthy adults administered single or multiple doses of AP showed no clinically significant interactions between atovaquone, proguanil, or its metabolite cycloguanil; thus, the pharmacokinetic parameters are similar to those of the drugs used as single agents. Atovaquone is highly lipophilic with low aqueous solubility and is therefore poorly absorbed unless consumed with a fatty meal. Co-administration of atovaquone and a fatty meal leads to a 5-fold increase in maximum plasma concentration (C\text{max}) over fasting. When taken with food, atovaquone displays linear pharmacokinetics, with a mean absolute bioavailability of 23%, but this varies significantly between individuals. Atovaquone is highly protein bound (> 99%) and has an apparent volume of distribution (V/F) in adult and pediatric populations of 8.8 L/kg. Atovaquone undergoes little if any metabolism, with 94% of the drug excreted unchanged in the feces and 0.6% in the urine. Atovaquone has a reported elimination half-life of 2–3 days in adults and 1–2 days in children, which is reportedly unaffected by dose, administration of food, or co-administration of proguanil. However, more recent data indicates that the half-life of atovaquone may be considerably longer than these initial reports (D. Kyle, personal communication).

Proguanil is rapidly absorbed from the gastrointestinal tract and achieves peak plasma concentrations in 2–4 hours, with an absolute bioavailability as high as 60%. Proguanil is 75% protein bound, and this binding is unaffected by the presence of atovaquone and vice versa. Proguanil is extensively distributed in tissues, with an apparent V/F in individuals > 15 years of age and between 31 and 110 kg of 1,617–2,502 L. In pediatric patients < 15 years of age weighing 11–56 kg, the V/F ranged from 462 to 966 L. Proguanil, but not cycloguanil, is concentrated in erythrocytes, hence the 5-fold difference in whole blood versus plasma concentration. Proguanil is metabolized to cycloguanil (primarily through CYP 2C19) and 4-chlorophenylbiguanide, with between 40% and 60% of proguanil excreted renally. The elimination half-life of proguanil is 12–21 hours in both adults and children but may be prolonged in slow metabolizers, as conferred by a genetic polymorphism in CYP 2C19.

**Pharmacodynamics.** Atovaquone is a hydroxynaphthoquinone that inhibits the development of liver stages of *Plasmodium* spp. When used as a single agent, however, over one third of individuals infected with *P. falciparum* will recrudesce; thus, atovaquone is not used as monotherapy for prevention or treatment. Proguanil, a biguanide, is also used in combination because of low efficacy as monotherapy. Both atovaquone and proguanil display causal activity against liver stages and activity against blood stages of *Plasmodium*.

Atovaquone inhibits parasite mitochondrial electron transport at the level of the cytochrome b1 complex and collapses mitochondrial membrane potential. Atovaquone selectively acts on parasite electron transport because of the 1,000-fold higher affinity of atovaquone for cytochrome *b* than cytochrome *bc1*. A small number of reported failures have been documented in non-immune travelers, with the remaining five occurring in semi-immune individuals. All published failures have occurred in patients whose malaria was acquired in Africa (Table 3).

**TABLE 3**

<table>
<thead>
<tr>
<th>Patient age, sex</th>
<th>Immune status</th>
<th>Dose, duration</th>
<th>Country of acquisition</th>
<th>Molecular marker of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>45, M34</td>
<td>Semi-immune</td>
<td>Four adult tabs daily, 3 days</td>
<td>Nigeria</td>
<td>Cyt b Tyr268Asn</td>
</tr>
<tr>
<td>24, F35</td>
<td>Non-immune traveler</td>
<td>Four adult tabs daily, 3 days</td>
<td>Kenya</td>
<td>Cyt b Tyr268Ser</td>
</tr>
<tr>
<td>28, M36</td>
<td>Non-immune traveler</td>
<td>Four adult tabs daily, 3 days</td>
<td>Mali</td>
<td>Cyt b Tyr268Ser</td>
</tr>
<tr>
<td>28, M37</td>
<td>Non-immune traveler</td>
<td>Four adult tabs daily, 3 days</td>
<td>Cameroon</td>
<td>Cyt b Tyr268Ser DHFR triple-codon mutation 51,59,108</td>
</tr>
<tr>
<td>1,5, M38</td>
<td>Non-immune traveler</td>
<td>One adult tab daily, 3 days</td>
<td>Ivory Coast</td>
<td>Wt cyt b and DHFR</td>
</tr>
<tr>
<td>4, M36</td>
<td>Non-immune traveler</td>
<td>One adult tab daily, 3 days</td>
<td>Ivory Coast</td>
<td>Cyt b Tyr268Ser DHFR triple-codon mutation 51,59,108</td>
</tr>
<tr>
<td>Adult, F38</td>
<td>Semi-immune</td>
<td>Four adult tabs daily, 3 days</td>
<td>Ivory Coast</td>
<td>Cyt b Tyr268Ser</td>
</tr>
<tr>
<td>38, F39</td>
<td>Semi-immune</td>
<td>Four adult tabs daily, 3 days</td>
<td>Democratic Republic of Congo</td>
<td>Wt cyt b</td>
</tr>
</tbody>
</table>
Table 4
Mild to moderate ADRs associated with AP prophylaxis and treatment

<table>
<thead>
<tr>
<th>Study location (design)</th>
<th>Sample size, dose, duration</th>
<th>Most frequent ADRs</th>
<th>Comparator</th>
<th>ADR risk with AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya (RDBPC, semi-immune)</td>
<td>108, One adult tab daily following 3-day curative course (four adult tabs daily), 10 weeks</td>
<td>Dyspepsia 6–12%  Gastritis 7–9%  Abdominal pain 4–7%  Diarrhea 3–4%  Nausea 0–3%</td>
<td>Placebo</td>
<td>No difference between AP and placebo</td>
</tr>
<tr>
<td>Gabon (RDBPC, semi-immune schoolchildren)</td>
<td>125, Standard weight-based prophylaxis following 3-day weight-based treatment course, 12 weeks</td>
<td>Abdominal pain 33%  Headache 14%  Vomiting 7%  Nausea 2%</td>
<td>Placebo</td>
<td>No difference between AP and placebo</td>
</tr>
<tr>
<td>Zambia (RDBPC, semi-immune)</td>
<td>136, one adult tab daily following 3-day curative course, 10 weeks</td>
<td>Headache 9%  Abdominal pain 5%  Diarrhea 3%</td>
<td>Placebo</td>
<td>ADRs more frequent in placebo</td>
</tr>
<tr>
<td>Irian Jaya (RDBPC, non-immune transmigrants)</td>
<td>148, one adult tab daily following 3-day curative course, 20 weeks</td>
<td>Headache  Dizziness  Abdominal pain  Arthropathy  Nausea</td>
<td>Placebo</td>
<td>Stomatitis and back pain more common in AP arm</td>
</tr>
<tr>
<td>Gabon (RDBPC, semi- and non-immune children, weight 11–40 kg)</td>
<td>165 Standard weight-based prophylaxis following 3-day treatment course with artesunate, 12 weeks</td>
<td>Headache 13%  Abdominal pain 13%  Cough 10%  Vomiting 5%  Fever 5%  Nausea 2%</td>
<td>Placebo</td>
<td>No difference between AP and placebo</td>
</tr>
<tr>
<td>Netherlands (RDBPC, healthy volunteers)</td>
<td>22, One adult tab daily, 14 days</td>
<td>Diarrhea 18%  Nausea 5%  Abdominal pain 5%  Headache 5%  Dizziness 5%  Nausea</td>
<td>Placebo</td>
<td>No difference between AP and placebo</td>
</tr>
<tr>
<td>South Africa (observational, open label, non-immune)</td>
<td>175, One adult tab daily, 10 weeks</td>
<td>Headache 7%  Abdominal pain 2%  Skin complaints 2%</td>
<td>No comparator</td>
<td>No comparator</td>
</tr>
<tr>
<td>Africa/South America (RDB, non-immune travelers)</td>
<td>511, One adult tab daily 2–5 weeks</td>
<td>Any GI 12%  Any neuropsychiatric 10%  Nausea 5%  Oral ulcers 4%  Vivid dreams 4%  Skin complaints 2%</td>
<td>CP</td>
<td>ADRs more common in CP group</td>
</tr>
<tr>
<td>Multicenter (RDB, non-immune travelers aged ≥ 3 years)</td>
<td>493, One adult tab daily or standard weight-based, 28 ± 8 days</td>
<td>Diarrhea 8%  Oral ulcers 6%  Abdominal pain 5%  Headache 4%  Nausea 3%  Vivid dreams 4%  Skin complaints 2%  Oral ulcers 4%</td>
<td>MQ</td>
<td>ADRs more frequent in MQ group</td>
</tr>
<tr>
<td>Multicenter (R, open-label, pediatric travelers, weight 11–50 kg)</td>
<td>110, Standard weight-based prophylaxis, 9–39 days</td>
<td>Diarrhea 22%  Abdominal pain 8%  Nausea 8%  Vomiting 7%  Headache 5%</td>
<td>CP</td>
<td>Similar frequency of ADRs between groups</td>
</tr>
<tr>
<td>Multicenter (RDB, non-immune travelers to sub-Saharan Africa)</td>
<td>164, One adult tab daily, 31–45 days</td>
<td>Neuropsych. 66%  GI 54%  Skin 21%</td>
<td>MQ</td>
<td>More neuropsych ADRs in MQ arm, more skin ADRs in CP arm</td>
</tr>
<tr>
<td>Eritrea (observational, open-label, non-immune soldiers)</td>
<td>184, One adult tab daily, 6 months</td>
<td>Diarrhea 32–44%  Abdominal pain/nausea/vomiting 28–34%  Headache 13–14%  Cough 10–12%  Anorexia 1–12%</td>
<td>DX</td>
<td>No comparator</td>
</tr>
<tr>
<td>Netherlands (observational, post-marketing surveillance, non-immune travelers)</td>
<td>154, One adult tab daily, 4–34 weeks</td>
<td>Diarrhea 18%  Abdominal pain 11%  Headache 9%</td>
<td>No comparator</td>
<td>No comparator</td>
</tr>
<tr>
<td>Treatment trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabon (R, open-label, semi-immune aged 15–65)</td>
<td>71, Four adult tabs daily, 3 days</td>
<td>Nausea 33%  Vomiting 29%  Abdominal pain 22%  Diarrhea 19%  Anorexia 8%</td>
<td>AQ</td>
<td>More complaints of nausea (33% vs. 13%) and abdominal pain (22% vs. 8%) in AP arm</td>
</tr>
<tr>
<td>Brazil (R, open-label, adult men)</td>
<td>77, Four adult tabs daily, 3 days</td>
<td>Abdominal pain 26%  Headache 22%  Nausea 16%  Dizziness 13%  Weakness 12%</td>
<td>Quinine + tetracycline</td>
<td>More ADRs (29/77 vs. 8/77; p &lt; 0.001) in QT arm</td>
</tr>
</tbody>
</table>
fold greater sensitivity of this system to atovaquone over the mammalian electron transport chain. Proguanil inhibits parasite dihydrofolate reductase (DHFR) primarily through the metabolite cycloguanil, with consequent interruption of folate cofactor and DNA synthesis. Both in vitro and in vivo studies have revealed the synergistic antimalarial action of AP, which leads to high cure rates of P. falciparum malaria, even in those with cycloguanil-resistant parasites conferred by DHFR mutations. The mechanism of synergy of proguanil with atovaquone is thought to be through its biguanide mode of action as opposed to through its metabolite. Proguanil has been shown to significantly enhance the ability of atovaquone to collapse mitochondrial potential by lowering the effective concentration of atovaquone needed to do so. Thus, proguanil is able to act synergistically with atovaquone in the setting of documented proguanil resistance or in those who are unable to metabolize proguanil to cycloguanil because of CYP 450 enzyme deficiencies.

Resistance to atovaquone can result from a single point mutation in parasite cytochrome b, which leads to reduced binding affinity for atovaquone. In the documented cases of AP treatment failure (Table 3), resistance has been associated with a single substitution at codon 268 of cytochrome b, resulting in a change from tyrosine to serine or tyrosine to asparagine. Resistance to proguanil involves the stepwise development of point mutations in the dhfr gene, which confer resistance to the metabolite cycloguanil. If cytochrome b mutations at codon 268 are present, the antimalarial activity of AP is dependent on cycloguanil’s antifolate activity, which is frequently compromised by the presence of dhfr mutations.

### COMPLIANCE

Few data are available on adherence to the recommended dosing schedule of AP outside of research settings. The majority of published studies used directly observed therapy or

### Table 4

Continued

<table>
<thead>
<tr>
<th>Study location (design)</th>
<th>Sample size, dose, duration</th>
<th>Most frequent ADRs</th>
<th>Comparator</th>
<th>ADR risk with AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand (R, open-label, adults)[26]</td>
<td>91, Four adult tabs daily, 3 days</td>
<td>Vomiting 10% Sore throat 8% Diarrhea 5% Abdominal pain 2%</td>
<td>MQ</td>
<td>Vomiting more likely in AP arm (10% vs. 2%)</td>
</tr>
<tr>
<td>Zambia (R, open-label, semi-immune aged 14–54)[24]</td>
<td>82, Four adult tabs daily, 3 days</td>
<td>Headache 28% Abdominal pain 28% Weakness 25% Diarrhea 16% Vomiting 12%</td>
<td>SP</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>Philippines (R, open-label, children &gt; 12 years, adults &lt; 65 years)[25]</td>
<td>55, 30–40 kg, three adult tabs daily &gt; 40 kg, four adult tabs daily, 3 days</td>
<td>Vomiting 18% Abdominal pain 15% Anorexia 11% Headache 6%</td>
<td>CQ</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>Multicenter (R, open-label, non-immune adults)[27]</td>
<td>25, Four adult tabs daily, 3 days</td>
<td>Vomiting 44% Nausea 24% Insomnia 16% Headache 16% Diarrhea 12%</td>
<td>HF</td>
<td>Vomiting more common in AP arm (44% vs. 4%)</td>
</tr>
<tr>
<td>Kenya (R, open-label, semi-immune children)[29]</td>
<td>84, Atovaquone 20 mg/kg/d, Proguanil 8 mg/kg/d, 3 days</td>
<td>Abdominal pain 12% Vomiting 16% Cough 12% Anorexia 11% Abdominal pain 10% Headache 10%</td>
<td>HF</td>
<td>Vomiting more likely in AP group (16% vs. 8%)</td>
</tr>
<tr>
<td>Thailand (R, open-label, aged 2–70 years)[28]</td>
<td>530, Four adult tabs daily, or 20/8 mg/kg/d, 3 days</td>
<td>Late vomiting 13% Nausea 9% Abdominal pain 5% Early vomiting 3%</td>
<td>AAP</td>
<td>Early vomiting greater in AP group (2.8% vs. 1.1% in AAP group)</td>
</tr>
<tr>
<td>Gabon (R, open-label, children aged 3–43 months, weight 5–11 kg)[30]</td>
<td>100, 20/8 mg/kg/d, 3 days</td>
<td>Cough 14% Diarrhea 12% Vomiting 7% Weakness 1%</td>
<td>AQ</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>Thailand, (observational, open-label, children aged 5–12 years)[39]</td>
<td>30, 20 mg/kg/d, 3 days</td>
<td>Headache 44% Anorexia 38% Abdominal pain 25% Insomnia 22%</td>
<td>No comparator</td>
<td>No comparator</td>
</tr>
<tr>
<td>Thailand, (observational, open-label, aged 15–52 years with P. vivax)[37]</td>
<td>46, Four adult tabs daily, 3 days</td>
<td>Vomiting 2%</td>
<td>No comparator</td>
<td>No comparator</td>
</tr>
<tr>
<td>Denmark (observational, open-label, semi- and non-immune adults)[30]</td>
<td>50, Four adult tabs daily, 3 days</td>
<td>Headache 36% Nausea 36% Vomiting 18% Dizziness 14% Neuropsych 7%</td>
<td>No comparator</td>
<td>No comparator</td>
</tr>
</tbody>
</table>
### Table 5
Severe adverse drug reactions associated with AP prophylaxis and treatment

<table>
<thead>
<tr>
<th>Study location (design)</th>
<th>Sample size, dose, duration</th>
<th>Severe ADRs/at risk</th>
<th>SAE</th>
<th>Discontinued because of severe adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prophylaxis trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya (RDBPC, semi-immune)⁹</td>
<td>108, One adult tab daily following 3-day curative course (four adult tabs daily), 10 weeks</td>
<td>0/108</td>
<td>—</td>
<td>Not documented</td>
</tr>
<tr>
<td>Gabon (RDBPC, semi-immune schoolchildren)¹¹</td>
<td>125, Standard weight-based prophylaxis following 3-day weight-based treatment course, 12 weeks</td>
<td>0/125</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Zambia (RDBPC, semi-immune)²⁰</td>
<td>136, One adult tab daily after 3-day curative course, 10 weeks</td>
<td>0/136</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Irian Jaya (RDBPC, non-immune transmigrants)¹⁶</td>
<td>148, One adult tab daily after 3-day curative course, 20 weeks</td>
<td>4/148</td>
<td>Abdominal pain 3 Exfoliative skin rash 1</td>
<td>Not documented</td>
</tr>
<tr>
<td>Gabon (RDBPC, semi- and non-immune children, weight 11–40 kg)¹²</td>
<td>165, Standard weight-based prophylaxis following 3-day treatment course with artesunate, 12 weeks</td>
<td>0/165</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Netherlands (RDBPC, healthy volunteers)</td>
<td>22, One adult tab daily, 14 days</td>
<td>0/22</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>South Africa (observational, open label, non-immune)¹³</td>
<td>175, One adult tab daily, 10 weeks</td>
<td>0/175</td>
<td>—</td>
<td>3 (2 headache, 1 nausea + dizziness)</td>
</tr>
<tr>
<td>Africa/South America (RDB, non-immune travelers)²⁰²⁰</td>
<td>511, One adult tab daily, 2–5 weeks</td>
<td>5/511</td>
<td>Allergic reaction</td>
<td>1</td>
</tr>
<tr>
<td>Multicenter (RDB, non-immune travelers aged ≥ 3 years)¹⁵</td>
<td>493, One adult tab daily or standard weight-based 28 ± 8 days</td>
<td>19/493</td>
<td>Neuropsych 9 Skin 2 GI 1</td>
<td>13 discontinued drug because of treatment-attributable AEs 6 “treatment-limiting”</td>
</tr>
<tr>
<td>Multicenter (R, open-label, pediatric travelers, weight 11–50 kg)¹²</td>
<td>110, Standard weight-based prophylaxis, 9–39 days</td>
<td>2/110</td>
<td>Not specified</td>
<td>0</td>
</tr>
<tr>
<td>Multicenter (RDB, non-immune travelers to Sub-Saharan Africa)²⁰</td>
<td>164, One adult tab daily, 31–45 days (All severe AEs)</td>
<td>11/164</td>
<td>Neuropsych 5 GI 5 Skin 2 Other 2</td>
<td>3 not necessarily drug related</td>
</tr>
<tr>
<td>Eritrea (observational, open-label, non-immune soldiers)²⁰</td>
<td>184, One adult tab daily, 6 months</td>
<td>0/184</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Netherlands (observational, post-marketing surveillance, non-immune travelers)²⁰</td>
<td>154, One adult tab daily, 4–34 weeks</td>
<td>0/154</td>
<td>Intractable diarrhea</td>
<td>2</td>
</tr>
<tr>
<td><strong>Treatment trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabon (R, open-label, semi-immune aged 15–65)²²</td>
<td>71, Four adult tabs daily, 3 days</td>
<td>0/71</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Brazil (R, open-label, adult men)²³</td>
<td>77, Four adult tabs daily, 3 days</td>
<td>— /77</td>
<td>Unknown</td>
<td>Not documented</td>
</tr>
<tr>
<td>Thailand (R, open-label, adults)²⁰</td>
<td>91, Four adult tabs daily, 3 days</td>
<td>0/91</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Zambia (R, open-label, semi-immune aged 14–54)²⁴</td>
<td>82, Four adult tabs daily, 3 days</td>
<td>0/82</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Philippines (R, open-label, children &gt; 12 years, adults &lt; 65 years)²⁵</td>
<td>55, 30–40 kg, three adult tabs daily &gt; 40 kg, four adult tabs daily, 3 days</td>
<td>0/55</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Multicenter (R, open-label, non-immune adults)²⁷</td>
<td>25, Four adult tabs daily, 3 days</td>
<td>3/25</td>
<td>Intractable vomiting</td>
<td>3</td>
</tr>
<tr>
<td>Kenya (R, open-label, semi-immune children)²⁹</td>
<td>84, Atovaquone 20 mg/kg/d, Proguanil 8 mg/kg/d, 3 days</td>
<td>6/84</td>
<td>Rash 3 Vomiting 1</td>
<td>One caused by repeated vomiting</td>
</tr>
<tr>
<td>Thailand (R, open-label, aged 2–70 years)²⁸</td>
<td>530, Four adult tabs daily, or 20/8 mg/kg/d, 3 days</td>
<td>0/530</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Gabon (R, open-label, children aged 3–43 months, weight 5–11 kg)²⁹</td>
<td>100, 20/8 mg/kg/d, 3 days</td>
<td>0/100</td>
<td>—</td>
<td>One withdrawal from study because of repeated vomiting</td>
</tr>
</tbody>
</table>

BOGGILD AND OTHERS
controlled administration of the drug. In general, risk factors for poor adherence to recommended dosing schedules include daily, twice weekly, or thrice weekly dosing compared with once weekly regimens,\(^9\) duration of travel > 4 weeks, age of user < 40 years, and the subjective association of the antimalarial with an adverse event.\(^6^0\) That AP is recommended for only 7 days after travel should theoretically raise adherence to this regimen over other antimalarials that are taken for 4 weeks after travel. This is supported by the findings from a study among non-immune travelers to malarious areas where 93% of persons on AP reported taking the prescribed post-travel dose (defined as being adherent to \(\geq 80\)% of the prescribed doses) compared with 80% of persons on CP (\(P = 0.001\)).\(^1^4\) In another prophylaxis trial, the proportion of participants who took \(\geq 80\)% of prescribed doses in the post-travel period was higher in the AP arm (88%) than in the MQ arm (70%; \(P = 0.001\)).\(^1^5\) In a multicenter comparative prophylaxis trial in non-immune pediatric travelers, a similar trend was found. Whereas pre- and intra-travel adherence rates were comparable (98% versus 99%), post-travel adherence was higher in the AP arm (97%) compared with the CP arm (87%).\(^1^7\)

### SAFETY AND TOLERABILITY

In general, atovaquone and proguanil have a history of excellent tolerability as single agents. Atovaquone has been used for over a decade in the treatment of Pneumocystis jiroveci pneumonia in HIV-1–positive individuals at a dosage of 750 mg, three times a day, for 21 days, with low rates of reported side effects.\(^6^1\) Similarly, proguanil has been used for decades as a long-term malaria prophylactic and in pregnant and breast-feeding women with low rates of adverse events.\(^6^2\) The combination AP seems to be well tolerated at both prophylactic and treatment doses, with abdominal pain, nausea, vomiting, diarrhea, and headache being the most frequently cited side effects (Table 4). Mild-moderate and severe ADRs are summarized in Tables 4 and 5, respectively.

#### Prophylaxis

At prophylactic doses, AP has an excellent safety profile, with gastrointestinal (GI) disturbances and headache the most frequently cited ADRs (Table 4). In four of six placebo-controlled prophylaxis trials, there were no significant differences in ADRs (mild, moderate, severe) between the AP arm and placebo group.\(^9\)\(^,\)\(^1^1\)\(^,\)\(^1^2\)\(^,\)\(^6^6\) In one placebo-controlled trial, ADRs in general were more common in the placebo group, and again, were primarily GI related.\(^1^0\) In another placebo-controlled trial, stomatitis and back pain were reportedly more common in the AP group, although the treating physician did not feel that the back pain was necessarily drug-related.\(^1^6\) Importantly, no difference in the frequency of vomiting was reported among those receiving AP prophylaxis or placebo control.\(^1^1\)

Two randomized comparative trials have evaluated the safety and tolerability of AP prophylaxis in non-immune adults. Hogh and others\(^1^4\) showed that those in the AP arm had a lower frequency of treatment-related GI adverse events (12% versus 20%, \(P = 0.001\)) and of treatment-related adverse events of moderate-severe intensity (7% versus 11%, \(P = 0.05\)) compared with those in the CP arm. In addition, there were fewer treatment-related adverse events that caused prophylaxis to be discontinued in the AP arm compared with the CP arm (0.2% versus 2%, \(P = 0.015\)).\(^1^4\) In their randomized comparison of four malaria prophylactic agents (AP, CP, doxycycline [DX], and MQ), Schlagenhauf and others\(^6^5\) showed that AP was associated with a low proportion of mild-moderate adverse events (32% versus 45% CP, 42% MQ, 33% DX) and severe events (7% versus 12% MQ, 11% CP, 6% DX). In addition, a high proportion of travelers (85%) reported some adverse event during the initial placebo run-in phase, and the incidence of AEs in placebo users was comparable with that in the medication arms.\(^6^5\) A third randomized double-blind comparative trial examined the safety and tolerability of AP prophylaxis in non-immune children and adults.\(^1^5\) Although adverse events were reported by an equivalent proportion of subjects (71.4% AP versus 67.3% MQ), those in the AP arm had fewer treatment-related neuropsychiatric ADRs (14%) compared with those receiving MQ (29%, \(P = 0.001\)).\(^1^5\) Participants in the AP arm also suffered fewer ADRs of moderate-severe intensity (10% versus 19%, \(P = 0.001\)) and fewer ADRs that led to discontinuation of prophylaxis (1.2% versus 5%, \(P = 0.001\)).\(^1^5\)

One randomized, multicenter, open-label, comparative prophylaxis trial has evaluated the safety and tolerability of

<table>
<thead>
<tr>
<th>Study location (design)</th>
<th>Sample size, dose, duration</th>
<th>Severe ADRs/at risk</th>
<th>SAE</th>
<th>Discontinued because of severe adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand (observational, open-label, children aged 5–12 years)(^6^9)</td>
<td>30, 20 mg/kg/d, 3 days</td>
<td>0/30</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Thailand (observational, open-label, aged 15–52 years with (P. ) vivax)(^1^9)</td>
<td>46, Four adult tabs daily, 3 days</td>
<td>0/46</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Denmark (observational, open-label, semi- and non-immune adults)(^7^0)</td>
<td>50, Four adult tabs daily, 3 days</td>
<td>0/50</td>
<td>—</td>
<td>0</td>
</tr>
</tbody>
</table>
AP in pediatric travelers. Compared with CP, fewer participants in the AP arm had treatment-related ADRs (8% versus 10%), including GI complaints (5% versus 10%). The only two subjects who discontinued prophylaxis because of drug-related adverse events were CP users.

The transient elevation of hepatic transaminases observed at treatment doses of AP do not seem to occur in those taking standard prophylactic regimens (one adult tablet daily). Safety trials that have evaluated clinical biochemistries such as alanine aminotransferase (ALT) and alkaline phosphatase have shown no differences in chemistry or hematologic values between those receiving AP prophylaxis and placebo, or CP. Severe ADRs leading to discontinuation of prophylaxis are uncommon with AP and were documented in 12 of 2,611 at-risk individuals from 13 studies of prophylaxis. Alkylation, pruritic or exfoliative skin rash or urticaria were documented in five participants receiving AP prophylaxis, whereas severe abdominal pain or diarrhea occurred in three and two participants, respectively. Severe GI ADRs that did not necessarily limit the use of AP prophylaxis were recorded in six other individuals. Histologically confirmed Stevens-Johnson Syndrome associated with AP has been described in a 65-year-old man who became symptomatic within days of initiating prophylaxis. One episode of acute hepatitis has also been reported in association with AP prophylactic use.

**Treatment.** Nine randomized, open-label treatment trials report on the safety and tolerability of AP used for the management of uncomplicated P. falciparum malaria. Six of these trials enrolled adults, one trial enrolled both children and adults, and two randomized trials were performed in children exclusively. Another two observational treatment studies reported on the safety and tolerability of AP and a third observational study examined the safety and tolerability of AP when used for treatment of P. vivax malaria. Three randomized treatment trials were conducted in known semi-immune individuals. AEs reported in these trials are summarized in Tables 4 and 5.

In general, AP is as well or better tolerated than other medications used in the treatment of malaria. Notably, AP was better tolerated than the traditional treatment regimen in North America, quinine plus tetracycline. Treatment-limiting ADRs for AP are rare (Table 5), occurring in < 1% of patients taking treatment doses. The most frequently reported ADRs associated with treatment doses of AP include nausea, vomiting, and abdominal pain. Headache and cough are also commonly documented side effects during treatment trials. In most cases, these ADRs are mild in nature and do not interfere with treatment. Vomiting may be the exception to this rule. In four randomized, comparative treatment trials, vomiting occurred at a significantly greater frequency in the AP arm than in other arms (range, 2.8–44% AP arms versus 1.1–8% comparators). In four trial participants, vomiting was considered severe, and in two individuals, vomiting either limited therapy or resulted in withdrawal. However, this risk of severe or treatment-limiting vomiting caused by AP is still small, documented in 5 of 1,241 at-risk individuals (0.4%). In most cases, vomiting can be overcome with intercurrent antiemetics and/or re-administration of AP.

Elevation of hepatic transaminases (ALT, aspartate aminotransferase [AST]) has been documented in recipients of AP treatment at a greater frequency than those receiving MQ, although these elevations were transient in nature, resolving in most by 28 days. The clinical significance of such elevations is unknown, although treatment-limiting perturbations in liver function tests have been reported.

**CONTRAINDICATIONS**

AP is contraindicated in those who have a known hypersensitivity to either atovaquone or proguanil. One case of anaphylaxis has been documented in a patient receiving AP for treatment of uncomplicated falciparum malaria. AP is further contraindicated in persons with severe renal impairment (CrCl < 30 mL/min).

**DURATION OF USE**

In North America, there is no stated limit on duration of use of AP as a prophylactic agent, whereas in much of Europe, AP is only approved for up to 4 weeks of travel. Few data exist on the adherence, safety, or tolerability of long-term AP use. A randomized prophylaxis trial administered AP to participants for up to 20 weeks, and two observational prophylaxis studies have reported daily use of AP for 26–34 weeks, all with excellent tolerability. One study reported adherence to AP prophylaxis among 184 non-immune soldiers stationed in Eritrea. Only 42% of these soldiers reported ≥ 75% compliance with daily dosing, with a lack of perceived risk of malaria and difficulty remembering daily intake with a meal cited as the most common reasons for poor adherence. As single agents, atovaquone and proguanil have been used with good tolerability for much longer periods of time. For instance, proguanil (often in the form of CP) has been used as malaria prophylaxis for up to 2 years in Peace Corps volunteers, 3 years in children of expatriates living in Cameroon, and 2.5 years in French expatriates residing in Rwanda. Similarly, atovaquone has been used as prophylaxis against P. jirovecki pneumonia in HIV-infected individuals for up to 2 years. One clinical trial compared the protective efficacy of atovaquone to dapsone for P. jirovecki pneumonia prevention and followed participants for a median of 27 months. The frequency of ADRs was similar between groups, and most were gastrointestinal in nature. A recent trial in HIV–infected children compared atovaquone plus azithromycin versus trimethoprim-sulfamethoxazole for the long-term prevention of serious bacterial infections. The median duration of follow-up was 3 years, and both therapies had similar adverse event profiles.

Another clinical trial compared the protective efficacy of atovaquone to aerosolized pentamidine for P. jirovecki pneumonia prophylaxis, with a median duration of prophylaxis of 26 weeks. In this trial, the frequency of treatment-limiting ADRs was highest in the atovaquone groups: 25% in the 1500 mg arm, 16% in the 750 mg arm, and 7% in the pentamidine group. One patient in the 1,500 mg atovaquone group developed elevation of hepatic transaminases, which was attributed to the drug.

**THERAPEUTIC INDEX AND OVERDOSE**

The fixed combination of AP consists of 250 mg atovaquone and 100 mg proguanil hydrochloride per adult tablet.
The recommended adult dosages for prophylaxis and treatment are one and four tablets per day, respectively. Up to 31.5 g of atovaquone have been consumed with few resultant signs or symptoms. Likewise, overdoses of up to 15 g of proguanil have resulted in no long-term sequelae, and doses as high as 1,400 mg/d for a duration of 2 weeks have been tolerated without apparent toxicity.

**DRUG INTERACTIONS**

Plasma concentrations of atovaquone are significantly reduced with concomitant administration of tetracycline (40% reduction), rifampin (50% reduction), and rifabutin (34% reduction). Although there is a pharmacokinetic interaction between tetracycline and atovaquone, of note, in the initial dose-ranging studies performed with atovaquone for antimalarial use, both proguanil and tetracycline were chosen as potential drugs for use in combination because of laboratory evidence of potentiation. Doxycycline was chosen because of its longer half-life. Clinical studies confirmed improved cure rates with combinations of proguanil, tetracycline, and doxycycline compared with atovaquone alone. Proguanil was selected as the preferred drug partner because of its long record of safety and the ability to use the drug in pregnant women and children. The combination of atovaquone and tetracyclines has been found to be efficacious in the treatment of falciparum malaria. Metoclopramide reduces both the bioavailability and absorption of atovaquone and should only be used if no other anti-emetics are available.

Atovaquone seems to increase plasma concentrations (area under the curve [AUC]) of zidovudine by inhibiting its glucuronidation. It also seems to modestly increase the etoposide AUC when the drugs were co-administered to children with acute lymphoblastic leukemia; in vitro, atovaquone inhibited etoposide catechol formation in microsomes. The authors point out that, although these pharmacokinetic effects are modest, they are potentially important because the risk of etoposide-related secondary acute myeloid leukemia has been linked to minor changes in schedule and concurrent therapy. Atovaquone lowered azithromycin’s maximum plasma concentration and steady-state values when the drugs were co-administered to HIV-1–positive children. The clinical implications are not known.

Atovaquone is highly protein-bound (≥ 99%) but does not displace other highly protein-bound drugs in vitro, indicating significant drug interactions arising from displacement are unlikely. Proguanil is metabolized primarily by CYP2C19. Potential interactions between proguanil or cycloguanil and other drugs that are CYP2C19 substrates or inhibitors are unknown.

**SPECIAL POPULATIONS**

**Children.** As summarized above, AP is efficacious in the prevention and treatment of *P. falciparum* malaria in pediatric populations when used in standard prophylactic and curative doses. Two randomized prophylaxis trials and two randomized treatment trials have been conducted exclusively in pediatric populations. Another three randomized trials (two prophylaxis studies included children > 11 kg, one treatment study included children > 10 kg) included children in their study population. As with adult populations, high protective efficacy and cure rates of *P. falciparum* malaria were observed: 97–100% protective efficacy in prophylaxis trials and 94–97.2% cure rates in treatment trials. These trials also confirmed that AP is equally well tolerated and is safe in pediatric populations. Common ADRs were those seen in adults and include abdominal pain, nausea, vomiting, and diarrhea. In one pharmacokinetic study, 27 HIV-1–positive children 1 month to 12 years of age tolerated atovaquone well. In six children younger than 10 years of age who were given atovaquone as part of an investigational *P. jiroveci* pneumonia treatment protocol, no ADRs were reported.

The pharmacokinetics of atovaquone are age dependent, and the elimination half-life of atovaquone is shorter in children. The pharmacokinetics of proguanil and cycloguanil are similar in adult and pediatric recipients. However, in clinical trials, plasma trough levels of atovaquone and proguanil in pediatric patients weighing 5–40 kg were within the range observed in adults after dosing by body weight.

**Pregnant women.** AP is classified as a pregnancy category C drug. An insufficient number of well-controlled studies of atovaquone or proguanil during pregnancy exist. However, proguanil as a single agent has been used as a malarial prophylactic for decades with no known toxic effects on the fetus. Animal trials have revealed a lack of teratogenicity of atovaquone, and adverse fetal outcomes were observed only at doses sufficiently high to cause maternal toxicity.

Three small published studies have reported on the safety, efficacy, and in one case, pharmacokinetics of AAP used as rescue therapy for multidrug resistant (MDR) *P. falciparum* malaria in pregnant women. Plasma concentrations of atovaquone, proguanil, and cycloguanil were measured in 24 pregnant Thai women before and after completing a 3-day course of atovaquone 20 mg/kg/d + proguanil 8 mg/kg/d + artesunate 4 mg/kg/d. Oral clearance and apparent volume of distribution for both atovaquone and proguanil were approximately twice that reported in non-pregnant adults, with and without acute malaria. Conversely, plasma concentrations were less than one half that observed previously in non-pregnant adults, although *t* max was similar between pregnant and previously reported non-pregnant adults. Elimination half-life of both atovaquone and proguanil was prolonged.

In the first published trial of AAP in pregnancy for MDR *P. falciparum* malaria, 27 pregnant Karen women were enrolled after multiple recrudescence *P. falciparum* infections that were resistant to standard therapies. The triple combination was administered at the following doses for 3 days: artesunate 4 mg/kg/d, atovaquone 20 mg/kg/d, and proguanil 8 mg/kg/d. The treatment was well tolerated, with dizziness, abdominal pain, and headache being the most frequently cited ADRs. None of the 27 women had recrudescence infection during the 42-day follow-up period. One patient recrudesced at day 63 and was cured with artesunate and clindamycin. All 27 women delivered live, singleton babies, and there were no congenital anomalies documented. Mean gestational age at delivery was 39 ± 2.2 weeks, and 22.7% of babies were classified as low birth weight (< 2,500 g; Table 6). In a more recent trial, 81 pregnant women in their second or third trimester with uncomplicated *P. falciparum* or mixed vivax-falciparum malaria were randomized to 3-day treat-
ment with AAP (N = 39) or 7-day treatment with quinine (N = 42), and followed for 42 days. Treatment failure was significantly more likely in the quinine arm than in the AAP arm (37% versus 5%, P = 0.001). There were no severe ADRs—the one maternal death was caused by a ruptured liver abscess. Mild-moderate ADRs were similar between groups, with the exception of tinnitus that was reported more frequently in the quinine arm (79.3% versus 24.1%). Of the 74 evaluable women at delivery (7 women moved before delivery), 73 women delivered singletons, and 1 woman delivered twins. There were no significant differences between AAP and quinine with respect to mean birth weight (8,332 versus 8,568 g), prematurity (11.8% versus 15.8%), intrauterine growth restriction (IUGR) (7.4% versus 12%), or estimated gestational age at delivery (39 versus 38.8 weeks). Growth and developmental parameters between the two groups of infants were similar at 1 year. Three congenital anomalies were documented (two in the AAP arm and one in the quinine arm), none of which were felt to be drug related (Table 6). To summarize, these small but important studies suggest that AAP use in pregnancy is safe, well tolerated, and without significant toxicity to the fetus. However, additional prospective studies are required to further investigate these issues, and AAP is not currently recommended for use during pregnancy.

It is not known whether atovaquone is excreted in human breast milk. Proguanil is excreted into breast milk in small quantities. Because of limited data on the safety of AP in children weighing < 5 kg, the use of AP is only recommended if mothers are nursing infants who weigh > 5 kg.

**Medical conditions.** Population-based pharmacokinetic studies have shown that sex, age, and intercurrent medication use do not appreciably affect the absorption or distribution parameters of atovaquone and proguanil. In the elderly with intact renal function, no dose adjustment is required.

### Table 6

**Safety of AP use in pregnancy**

<table>
<thead>
<tr>
<th>Study location (design)</th>
<th>Sample size</th>
<th>Dosing regimen, duration of dosing</th>
<th>Gestational age at AP initiation</th>
<th>Maternal and fetal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand (prospective, open-label trial of AAP in pregnant women)</td>
<td>27</td>
<td>AAP—4/20/8 mg/kg/day, 3 days</td>
<td>Median 28.2 weeks, range—1.6–37.3 weeks, 3 in first trimester</td>
<td>0 recrudescence at 42 days, 27 live-born singletons, 0 congenital anomalies, mean birth weight 2670 ± 453 g, percent low birth weight 22.7, mean gestational age 39 ± 2.2 weeks</td>
</tr>
<tr>
<td>Thailand (R, open-label trial of AAP in pregnant women, comparator quinine, (N = 42))</td>
<td>39</td>
<td>AAP—4/20/8 mg/kg/day, 3 days</td>
<td>Mean 21 ± 5.3 weeks, range 10.1–36.2 weeks</td>
<td>Cure rate at delivery: 94.9% (81.4–991%) AAP vs. 63.4% (46.9–77.4%) Q, 73 live-born singletons + 2 twins born to 74 evaluable women, no difference between AAP &amp; Q regarding congenital anomalies (2 vs. 1), prematurity (11.8% vs. 15.8%), or IUGR (12% vs. 7.4%), mean birth weight 2763 ± 550 g, mean gestational age at delivery 39 ± 2 weeks</td>
</tr>
</tbody>
</table>

The pharmacokinetics of atovaquone, proguanil, and cycloguanil have been examined in 13 patients with mild to moderate hepatic dysfunction (classified according to Child-Pugh) and compared with 13 healthy controls. The AUC and C\text{max} values for atovaquone in those with mild to moderate hepatic dysfunction were similar to those in healthy volunteers. The elimination half-life, however, was prolonged in patients with moderate hepatic dysfunction. Peak plasma concentration AUC and the elimination half-life of proguanil were increased in patients with mild to moderate hepatic dysfunction compared with healthy controls. Consequently, cycloguanil C\text{max} and AUC were decreased and half-life was prolonged. In persons with mild to moderate hepatic dysfunction, the manufacturer recommends no dose adjustment. The pharmacokinetics of AP have not been examined in those with severe hepatic dysfunction.

A single dose of AP in patients with mild to moderate renal failure results in an oral clearance and AUC for atovaquone, proguanil, and cycloguanil that are similar to those observed in healthy volunteers. However, in those with severe renal disease (CrCl < 30 mL/min), atovaquone C\text{max} and AUC are reduced, whereas elimination half-life and AUC of proguanil and cycloguanil were longer and higher, respectively. Thus, the potential for accumulation of these compounds makes them unsafe in those with severe renal dysfunction, hence the contraindication. In patients with chronic renal failure given proguanil, megaloblastic anemia and pancytopenia have been reported. The manufacturer recommends no dose adjustment in persons with mild to moderate renal impairment (CrCl = 30–90 mL/min).

### Table 7

**Cost of anti-malarial drugs**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cost for 14-day stay including recommended pre- and post-travel doses*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primaquine</td>
<td>$47.61</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>$39.76</td>
</tr>
<tr>
<td>Doxycycline—generic</td>
<td>$11.00</td>
</tr>
<tr>
<td>Vibra-Tabs (Pfizer)</td>
<td>$142.28</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>$84.64</td>
</tr>
<tr>
<td>AP</td>
<td>$113.39</td>
</tr>
</tbody>
</table>

* Data taken from Bryan, 2006 with permission.
Kline. This statement is made in the interest of full disclosure and not because the author considers this to be a conflict of interest.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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