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Discontinuing atovaquone/proguanil prophylaxis ad-hoc post-exposure and during-travel dose-sparing prophylactic regimens against *P. falciparum* malaria: An update with pointers for future research

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ABSTRACT

Background: Atovaquone/proguanil (AP) is a highly effective malaria chemoprophylaxis combination. According to current guidelines, AP is taken once daily during, and continued for seven days post exposure. A systematic review by Savelkoel et al. summarised data up to 2017 on abbreviated AP regimens, and concluded that discontinuing AP upon return may be effective, although the available data was insufficient to modify current recommendations. The same applies to other studies evaluating during-travel dose-sparing regimens.
Methods: A literature search in Pubmed and Embase was performed including search terms related to AP prophylaxis and pharmacokinetics to search for recent studies on abbreviated AP regimens published since 2017.
Results: Since the 2017 review, no new studies assessing discontinuing AP ad-hoc post-exposure prophylaxis have been published. Two new studies were identified assessing other abbreviated AP regimens; one investigated a twice-weekly AP regimen in 32 travellers, and one a three-day AP course in therapeutic dose (1000/400 mg) prior to exposure in 215 travellers. No malaria cases were detected in the study participants adhering to these regimens.
Conclusions: Further research would be needed if the research question is considered of sufficient importance to facilitate evidence-based decision-making to modify current guidelines, as efficacy studies in travellers are fraught with confounders. We recommend human challenge trials to study abbreviated AP regimens pertaining to malaria chemoprophylaxis as they allow for rational, subject number, time- and cost-saving trial designs.

1. Background

Atovaquone/proguanil (AP; brand names Malarone, Malanil, and others) is mostly well-tolerated and highly effective - both as malaria therapy and as chemoprophylaxis [1]. The currently approved AP malaria chemoprophylaxis regimen consists of one daily tablet containing 250 mg of atovaquone and 100 mg of proguanil, starting one day prior to departure to an endemic region and continuing up to seven days after return. The combination of atovaquone and proguanil is active against both pre-erythrocytic and erythrocytic stages of *Plasmodium* species [2–6], while most antimalarial drugs only have suppressive effects on erythrocytic stages [7]. As merozoites are released from the liver into the bloodstream only after 7–9 days, antimalarials with no anti-liver stage activity need to be continued for more than one week to

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maintain plasma concentrations required to fully suppress infections emerging from the liver [7]. AP, on the other hand, has full causal prophylactic activity, i.e., killing malaria parasites during the 5–9 days lasting initial hepatic stage [2–6]. This would allow earlier discontinuation. At the moment, the recommendation is to administer AP for seven more days after leaving an endemic area [2,7]. However, the need to cover the full duration of a *P. falciparum* liver stage by continuing AP for seven days has been questioned by some [8–10]. As sporozoites are thought to enter the liver within 30 min after inoculation [7], and in view of *P. falciparum* parasites being already susceptible to AP during the onset of the liver stage, one could argue that there might be no need for continuing AP prophylaxis after leaving an endemic area to achieve optimal post-travel protection.

A systematic review by our group by Savelkoel et al. summarised data up to 2017 on the prophylactic efficacy of abbreviated AP schedules focusing on discontinuing AP on the day of return and data supporting the current seven-day post-travel regimen. The authors concluded that there is limited direct and indirect evidence suggesting that an abbreviated regimen may be effective [8]. Hence, additional research would still be required before a shortened post-travel AP regimen, or any other drug-sparing prophylactic regimen could be implemented in practice based on unambiguous trial results. There is a rationale to resolve pertaining open questions by means of (a) clinical trial(s), as early discontinuation of AP after return from an endemic area would be more economical and attractive for travellers, and could potentially enhance adherence, with the same applying to dose-sparing regimens during travel. In this updated (non-systematic) review, we attend to new evidence possibly arising since the 2017 review on this topic [8]. Furthermore, from today's perspective, we reflect on how further research could be designed in order to yield an answer within a reasonable time frame, and with a reasonable use of resources in relation to the (somehow limited) importance of the research question, and in relation to a potential novel approach to making state-of-the-art malaria chemoprophylaxis feasible in a cost-effective way.

2. Methods

To update the earlier overview on studies assessing the efficacy and pharmacokinetics of abbreviated prophylactic AP schedules [8] also incorporating work on other (during-travel, dose-sparing regimens), PubMed and Embase were searched for studies published from 2017 up to January 13th, 2022. The same search strategy was applied as used by Savelkoel et al. [8], including search terms related to AP prophylaxis and pharmacokinetics (see Supplementary Table 1 for full search strategy). Articles were screened on title and abstract, and, if relevant, selected to assess full text. Additionally, reference lists of relevant articles were assessed. Of the included studies, the following data were extracted: first author; publication year; study design; number and characteristics of study participants; schedule and dose of AP; endemic region visited; and assessment of efficacy and outcome. If no dose of AP was noted, we assumed use of the standard prophylactic dose of 250 mg/100 mg.

3. Results

The search yielded a total of 257 articles. After removal of duplicates, 198 articles remained, that we assessed on title and abstract. Of these articles, ten articles were selected to assess full text, of which two studies were included in this review [11,12]. No additional studies were obtained by searching reference lists (see Supplementary Fig. 1 for flow chart of study selection). The two included studies were both not conducted on early post-travel AP discontinuation, but investigated other abbreviated AP schedules; Biber et al. investigated a twice-weekly AP regimen and Lau et al. investigated a three-day AP course in therapeutic dose (1000/400 mg) prior to exposure [11,12]. No studies were found assessing AP discontinuation ad-hoc post-exposure.

The study by Biber et al. was conducted in adult travellers to sub-Saharan Africa, who were a mean 6.2 months at risk. No malaria cases were detected among the 32 study participants taking AP twice weekly, whilst two out of four subjects in the no-prophylaxis group developed falciparum malaria [11]. The study by Lau et al. assessed a treatment course of AP as pre-travel malaria prophylaxis in 215 adult travellers visiting endemic areas in Asia, the Pacific Islands, and South and Central America for less than four weeks. This short course of AP had a high compliance rate (210/215), was well tolerated, and no cases of malaria were detected in the study which may not be surprising considering the low malaria risk at these destinations. However, the study was not powered to assess efficacy, as it was designed to investigate compliance and tolerability of the short AP course. Therefore, all travellers to sub-Saharan Africa were excluded, as there is a higher risk of malaria in this region [12]. Characteristics and results of the two studies published since 2017 are shown in Table 1a and those of earlier studies are shown in Table 1b [10,14,16–19].

4. Discussion

Since the 2017 review by Savelkoel et al. [8], only two novel studies arose assessing abbreviated AP regimens that were both conducted in adults [11,12]; no studies were found investigating AP discontinuation on the day of return. Moreover, both included studies suffered from limitations. The number of travellers studied by Biber et al. was rather small; 32 travellers taking AP twice weekly versus a control group of four subjects taking no prophylaxis. Their risk for infectious bites is difficult to assess; for those eight individuals with non-specified destinations to West Africa, it might have been considerable, for the 20 (with one of them having also visited West Africa), a low risk might be assumed and consequently, as travellers visited different areas, there was non-homogeneity in exposure, causing confounding [11]. The study by Lau et al., studying a pre-travel AP treatment course, was constructed to assess tolerability of AP and was, as study subjects only visited low-endemic areas, not powered to assess effectiveness, moreover, given the half-life of AP being way too short to cover one week, let alone four weeks, the pharmacological rationale behind this approach is ill-understood [12]. A notable methodological shortcoming tied to observational field studies like these is the lack of potential to include a placebo/control group, as it would be unethical to send travellers to a malaria-endemic area without chemoprophylaxis and without a possibility of close monitoring during follow-up. Furthermore, there is no assurance of exposure in field studies and as highly reliable surrogate markers of exposure are lacking (with circumsporozoite antibodies not being sufficiently sensitive), it remains uncertain whether study participants were protected by chemoprophylaxis or simply encountered no malaria parasites. A well-designed multicentre non-inferiority field trial including thousands of travellers, comparing the short regimen to the currently registered regimen, might provide sufficient data. However, in the absence of comprehensive funding opportunities and a mismatch between resources needed and potential knowledge gain, such a study would be impossible to conduct, and as the abridged regimen includes taking less tablets, no interest is expected from the pharmaceutical industry.

Due to the obstacles tied to field studies on travellers, it is inevitable to explore other approaches. Safely-designed modern human *Plasmodium falciparum* challenge models, as performed up-to-date primarily in the framework of antimalarial vaccine development, can now be employed to overcome these obstacles [13]. Only five HCTs have been published so far on chemoprophylaxis [13]; of which one involving atovaquone [5] and one involving atovaquone-proguanil [14]. This methodology is a useful alternative to field studies because all study participants undergo a malaria sporozoite challenge with *Plasmodium falciparum*, so that exposure can be assured. Therefore, a drastically smaller number of study participants would be required than in field trials. Additionally, study participants are closely watched during

Table 1a
Study characteristics and results of studies on abbreviated AP schedules published since 2017.

Author, year	Study design	Study participants	AP dose and schedule	Region visited	Assessment of efficacy	Outcomes
Biber et al. *2019* [11]	Observational study	36 adult travellers (32 and 4 in group 1 and 2, respectively)	2 groups: 1) Twice-weekly AP (TWAP) 2) No prophylaxis	Sub-Saharan Africa	Follow-up up to 1 month after return to Israel	Adherence to TWAP 28/32; no malaria occurred in TWAP group. 2/4 subjects in no-prophylaxis group developed falciparum malaria
Lau et al., *2019* [12]	Single arm trial	215 adult travellers to malaria-endemic areas for ≤4 weeks	3-day AP 1000/400 mg	Asia, the Pacific Islands, and South/Central America (further specifics of these regions not described)	Self-reported occurrence of malaria	Compliance 210/215; no cases of malaria (of note, study was not statistically powered to assess effectiveness)

Table 1b
Study characteristics and results of previously reviewed material on abbreviated AP schedules.

Author, year	Study design	Study participants	AP dose and schedule	Exposure (challenge model or region visited)	Assessment of efficacy	Outcomes
Lachish et al., 2016 [16]	Observational surveillance study	122 long-term expatriates (33, 40, 63 in group 1, 2, 3, resp.; 14 subject contributed twice)	3 groups: 1) Twice-weekly AP 2) Mefloquine weekly 3) No prophylaxis	West Africa (jungles of Angola and Centro Medico La Paz, Malabo, Equatorial Guinea)	Self-reported occurrence of malaria	No cases of malaria in TWAP group (0/391 person-months); 2 malaria cases (2.06/1000 person-months) in mefloquine group and 16 malaria cases (11.7/1000 person-months) in no prophylaxis group
Leshem et al., 2014 [10]	Active surveillance and passive surveillance	485 travellers (421, 9, 55, in groups 1, 2, 3, resp.)	3 groups: 1) AP discontinued 1 day post-travel 2) AP continued 2–7 days post-travel 3) No AP prophylaxis or AP discontinued during travel	Sub-Saharan Africa (mostly Tanzania, Uganda and Kenya)	Retrospective telephone survey 1–6 months after travellers return (active surveillance); malaria cases reported to the ministry of Health in Israel (passive surveillance)	No occurrence of malaria in any of the subjects in the active surveillance study. Of the malaria cases in the passive surveillance study no subjects used AP as prophylaxis.
Deye et al., 2012 [14]	Randomised placebo-controlled, double blind trial	36 malaria-naïve volunteers (6 per study arm)	6 arms: 1) 250/100 mg on day −1 (=1 day prior to challenge) 2) 250/100 mg on day +4 3) 250/100 mg on day −7 4) 500/200 mg on day −7 5) 1000/400 mg on day −7 6) open-label infectivity controls	Challenge by *P. falciparum*-infected mosquitoes	90-day observation period with outpatient assessments on days −7, −6, −5, −1, 0, 1, 4–20, 23, 28, 42, 70 and 90 and blood smears and PCRs on day 6–20 and 23.	2/5 subjects receiving 250/100 mg on day −7, and 1/6 of subjects receiving 1000/400 mg on day −7 were microscopically diagnosed with malaria. All others subjects were protected. Parasitaemia in 6/6 infectivity controls.
Polhemus et al., 2008 [17]	Short report with data derived from the control group of clinical trial	80 malaria-immune adult volunteers living in an endemic area	3-day AP 1000/400 mg	Kisumu West District in Kenya	Passive detection of infection directly after dosing. From week 2 weekly malaria blood films began.	First case of *P. Falciparum* malaria occurred 32 days after completion of AP. After 17 weeks, 38/80 subjects had developed a *P. falciparum* parasitaemia
Shanks et al., 1999 [18]	Short report with data derived from clinical trials	65 adult volunteers living in an endemic area	3-day AP 1000/400 mg	Western Kenya, near Lake Victoria	Not described	First case of malaria - occurred 32 days after starting AP. 50% of subjects had developed malaria parasitaemia after 55 days
Lell et al., 1998 [19]	Randomised placebo-controlled study assessing prophylactic AP, with initial curative treatment	265 healthy schoolchildren aged 4–16 years. After initial curative treatment 125 entered AP group and 140 placebo group	3-day AP course; dose determined by children's weight: 11–20 kg 250/100 mg; 21–30 kg 500/200 mg; 31–40 kg 750/300 mg; over 40 kg 1000/400 mg	Lalala Public School in Lambaréné, Gabon	Weekly visits that included taking thick blood smears and body temperature	First positive blood smear occurred 4 weeks after the initial curative treatment

follow-up, for example with daily contact and highly sensitive parasitological examination techniques. For that reason, parasitaemia can be detected rather early, thus allowing timely treatment before participants become symptomatic. Moreover, the potential of this type of study for close monitoring brings an opportunity to add a placebo group. Due to these benefits, human challenge models, as already applied in some of the work described here, are now increasingly applied across a broad range of pathogens, and could play an important role in investigating a broader selection of infectious diseases, that are easily fully treated or self-limiting, but are difficult to study in the field [15]. We had concluded earlier [8] that a well-designed randomised clinical trial investigating the prophylactic efficacy of AP taken on the last day of exposure in a human *Plasmodium falciparum* challenge model is warranted to yield the definitive answer to the question as to whether AP can be discontinued upon return from a endemic area without the loss of post-travel protection; the same holds true for a full evaluation of drug-sparing regimens to offer full chemoprophylactic protection with less than once daily intake. Ideally, measurements of plasma concentrations of both atovaquone and proguanil would be part of the design in order to underpin clinical data with pharmacological evidence.

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Appendix A. Supplementary data

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