The Use of Artemether-Lumefantrine for the Treatment of Uncomplicated *Plasmodium vivax* Malaria

Quique Bassat*

Barcelona Centre for International Health Research (CRESIB), Hospital Clinic Universitat de Barcelona, Barcelona, Spain

**Abstract:** The long-standing dearth of knowledge surrounding *Plasmodium vivax*, the most widely distributed of the malaria species, merits urgent attention. A growing awareness of the true burden of this parasite and its potential to cause severe disease, and the identification of increasing parasite resistance in many areas of the world to chloroquine, the mainstay of vivax treatment, underscores the need to identify new and effective treatment strategies. Artemisinin-based combination therapies (ACTs) have been widely adopted as first-line treatment for *P. falciparum* malaria and would offer logistic benefits in areas of co-endemicity. However, while ACTs show high and similar efficacy against the blood stages of *P. vivax*, neither ACTs nor chloroquine are active against vivax hypnozoites and must be complemented with a full course of primaquine to eradicate dormant vivax hypnozoites and prevent relapses. Artemether-lumefantrine (AL), the most commonly deployed ACT, has shown rapid clearance of *P. vivax* parasitemia and fever. The relatively short half-life of lumefantrine would appear beneficial in terms of reducing risk of resistance when compared to other ACTs. However, it has a shorter capability to suppress vivax relapses or prevent de novo infections, which generally translates into comparatively lower in vivo short-term measures of efficacy (e.g., day 28 or day 42 uncorrected cure rates). Assuming that the different artemisinin derivatives have equivalent efficacy against vivax, differences between AL and other ACTs may be restricted to the duration of plasma therapeutic levels of the partner drug, a variable of limited clinical relevance, particularly in regions with low chloroquine transmission rates or in cases where primaquine is added to the regimen to prevent relapses. More rigorous assessment of the use of ACTs in general, and AL in particular, for the treatment of *P. vivax* infections, either alone or in combination with primaquine, is merited. In the meantime, AL treatment of vivax malaria may be a pragmatic choice for areas with chloroquine-resistant *P. vivax*, and in co-endemic areas where AL is already used routinely against *P. falciparum* and parasitological differentiation is not routinely performed or only clinical diagnosis is used.

**Introduction**

*Plasmodium vivax* infection persists as a major global health problem. It is more widely distributed than *P. falciparum* [1], with over 2.5 billion people living at risk and an estimated 80 to 300 million clinical cases each year [2,3]. It is common in Asia, Oceania, Central and South America and the Middle East [1,3], but its burden is also increasingly recognized in East Africa [4–6] and, more recently, in other African regions with reports from western African countries including Democratic Republic of the Congo, Côte D’Ivoire, and Equatorial Guinea [1,7]. The belief that the virtual absence of the red blood cell Duffy-positive phenotype among black Africans protects these populations against *P. vivax* infections [8] (the Duffy protein is thought to be necessary for the parasite’s invasion of reticulocytes) is under reconsideration [9], and it is now hypothesized that *P. vivax* may invade young red blood cells using alternative mechanisms [10].

Traditionally, *P. vivax* has been regarded as a benign infection. This idea, however, has recently been challenged [2,11–14], and the literature reflects increasing reports of vivax-attributable severe or even life-threatening illness [15–17]. Episodes of *P. vivax* infection should thus be regarded as potentially lethal and should prompt urgent treatment with effective antimalarial medication.

In the majority of settings, *P. vivax* coexists with *P. falciparum* [18–20]. Although the examination of thin blood slides using optical microscopy has traditionally been used for species differentiation, accurate species diagnosis is difficult, and ultimately may require highly specific PCR methods, not applicable in the daily clinical routine. The sensitivity of rapid diagnostic tests is limited when trying to differentiate between these two species, especially at low parasitemias, common in *P. vivax* infections [21,22]. In resource-challenged regions, empiric treatment based on clinical suspicion is widely accepted and implemented, although no longer recommended by the World Health Organization (WHO) [20].

Programmatically, the use of a single first-line therapy effective against both *P. vivax* and *P. falciparum* would be ideal in view of the frequent co-endemicity of the two species and the increasing resistance of parasites to chloroquine. The widespread adoption of artemisinin-based combination therapies (ACTs) as highly effective first-line therapy for *P. falciparum* has prompted a closer examination of their role in the management of *P. vivax* malaria. This article considers the available evidence relating to the potential role of artemether-lumefantrine (AL), the most widely used ACT worldwide, in the management of vivax malaria.

**Citation:** Bassat Q (2011) The Use of Artemether-Lumefantrine for the Treatment of Uncomplicated *Plasmodium vivax* Malaria. PLoS Negl Trop Dis 5(12): e1325. doi:10.1371/journal.pntd.0001325

**Editor:** David Joseph Diemert, The George Washington University Medical Center, United States of America

**Published:** December 27, 2011

**Copyright:** © 2011 Quique Bassat. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Funding:** QB has received speaker fees and payments from Novartis to attend meetings.

**Competing Interests:** QB received speaker fees and payments from Novartis to

* E-mail: quique.bassat@cresib.cat
Methods

An electronic search of articles published on or before 31 January 2011 was performed in EMBASE, Medline, PubMed, and BIOSIS Previews. Search terms were “artemether-lumefantrine,” “artemether,” “artemisinin,” “Plasmodium vivax,” and “vivax,” with no time or language restrictions. Search results were examined for clinical studies of AL in the treatment of uncomplicated P. vivax malaria, including subpopulation analyses. The limited number of relevant, well-designed trials meant that no meaningful meta-analysis could be performed.

P. vivax Life Cycle and Implications for the Evaluation of Efficacy of Antimalarials

In contrast to P. falciparum, P. vivax forms hypnozoites that can remain dormant in the parenchymal cells of the host liver following an acute infection. After an interval of time, which varies in duration depending on the geographical area [3], the hypnozoites can mature into hepatic schizonts that rupture to release merozoites capable of infecting erythrocytes and inducing a spontaneous relapse (Figure 1). Clinically, relapses present as a new malaria episode, indistinguishable from a new infection.

Thus, in P. vivax infections, the eradication of blood schizonts is not sufficient to control the disease, and an effective treatment requires killing the hypnozoites (“radical cure”) to prevent future relapses. Chloroquine, an inexpensive and effective treatment for vivax malaria in most areas of the world [23] has been the mainstay first-line therapy for this species for the past seven decades. It is still WHO’s recommended drug for vivax, but needs to be combined with primaquine, currently the only approved drug capable of achieving radical cure of hypnozoites [18,24,25]. WHO guidelines state that primaquine needs to be administered daily for 14 d to achieve this purpose [20], although the efficacy of shorter (7 d) courses is being investigated. Chloroquine achieves parasitological cure at day 20 in more than 90% of chloroquine-sensitive P. vivax infections [26], but in many areas of the world, significant levels of resistance to this drug in P. vivax have been documented [19,27,28], notably in Indonesia (<50% probability of therapeutic success) [19] and to a lesser extent in India [29], Myanmar [30], Turkey [31], the Brazilian Amazon [32], and Colombia [33]. Worryingly, there is also growing evidence of clinical resistance of vivax to chloroquine in Africa [34–36]. Emergence of resistance to chloroquine, particularly in view of the potentially serious consequences of vivax infection, adds a further urgency to providing effective therapy.

The possibility of relapse brings about uncertainty when assessing the efficacy of antimalarial drugs that have an effect on asexual stages of the life cycle but not on the dormant liver forms. Thus, patients correctly treated with an antimalarial with no antihypnozoite activity may present with recurrent post-treatment parasitemia that can derive from one of three sources: (1) reappearing parasites as a result of the incomplete clearance of the original infection (recrudescence), often the consequence of ineffective or incomplete treatment, (2) generation of de novo parasitemia from the liver reservoirs (relapse), or (3) parasites ensuing from a new and independent infection (new infection) (Figure 2). Parasites in recrudescent or relapsing infections may be genetically identical to the original infection and thus impossible to differentiate with current technology. Some reports state that over

![Figure 1. P. vivax life cycle and sites of action for different antimalarials.](https://www.plosntds.org/doi/10.1371/journal.pntd.0001325.g001)
half of the relapsing parasites may be genetically different from the preceding documented infection, but this may be explained by older heterologous hypnozoites becoming reactivated [37]. A new infection arising from the bite of an infected vector, however, may differ from the original infecting parasite such that they can be distinguished from one another by PCR molecular techniques. A pragmatic solution to this investigative hurdle has been adopted whereby any new parasitemia appearing before day 16 is by convention directly classified as recrudescence (i.e., treatment failure) because of the unlikelihood of the infection being a relapse within such a short space of time, and because this is the minimum incubation period for a new infection to appear in peripheral blood. Reappearance of parasites after day 16 cannot be assumed to be recrudescence [20].

**ACTs in Vivax Malaria**

ACTs are highly effective against uncomplicated *P. falciparum* malaria and are now recommended as first-line therapy [20], having been adopted in most countries where *P. falciparum* is endemic. Most ACTs show high and similar efficacy against the blood stages of *P. vivax* [38], but none is active against the hepatic *P. vivax* hypnozoites responsible for relapse [39]. Therefore, in order to achieve radical cure, similar to chloroquine treatment, ACT treatment must be complemented with a full course (14 d) of primaquine.

Where both *P. vivax* and *P. falciparum* species are prevalent and ACTs have been adopted as first-line therapy for *P. falciparum*, use of a unified first-line therapy based on ACTs would simplify treatment procurement, distribution, and management, offering interesting logistical benefits. ACT therapy for both types of infections would also avoid the problem of *P. falciparum* being mistakenly diagnosed as *P. vivax* and inadequately treated with chloroquine in the many regions where diagnosis is based on clinical symptoms alone [18]. In areas of chloroquine-resistant *P. vivax*, and where ACTs have already been adopted for the treatment of *P. falciparum* malaria, ACTs could also be used for the treatment of vivax, provided they are complemented with the standard primaquine course [20]. Indeed, at least four countries have now adopted a unified first-line therapy based on ACTs: the Solomon Islands, Vanuatu, and Papua New Guinea deploy AL, while Indonesia deploys dihydroartemisinin-piperaquine (DHA-PQP) in Papua [18].

**Rationale for Use of AL**

A large evidence base is now available to demonstrate the efficacy of AL in the treatment of uncomplicated malaria in a range of patient types and locations worldwide, but particularly for *P. falciparum* infections. This includes the most extensive data for any ACT in children and pregnant women [40–44], the two populations most vulnerable to malaria. AL also offers the most

---

*By convention never <16 days if originating from the same infection*
extensive safety data base of all ACTs [45], being the most widely used ACT for falciparum malaria worldwide, with over 400 million treatments having already been distributed. Moreover, it is the only ACT with a formulation specifically tailored to use in children that is recommended by WHO. Last, but not least, resistance to lumefantrine in field isolates has not yet been convincingly demonstrated, an important advantage attributed to the relatively short half-life of lumefantrine [46] and the fact that, in contrast to most other ACT partner drugs, lumefantrine has never been used as monotherapy.

**Impact of the Partner Drug’s Half-Life on Efficacy of ACTs in Vivax Infections**

ACTs in which the partner drug has a long half-life are theoretically considered preferable in vivax infections [20], since this would be expected to extend the period of prophylaxis against either new infections or latent ones ensuing from the dormant hypnozoites in the liver. In an analysis of 10,549 patients treated for falciparum malaria on the Thailand–Myanmar border during 1991–2005, 11% (n = 1,164) of whom had mixed falciparum/vivax infection at screening, the rate of P. vivax infection by day 63 was 12.0% (n = 1,269) for vivox monoinfection and 8.8% (n = 86) for mixed infections [47]. ACTs that included partner drugs with shorter half-lives increased the risk of vivax infection recurrence by day 63 after treatment for P. falciparum malaria: the more rapidly eliminated AL and artesunate-ataovaquine-proguanil combinations were associated with a 3.6-fold and 4.2-fold higher adjusted hazard ratio, respectively, for P. vivax infection than artesunate-mefloquine (p<.0001). No difference was observed for AL versus DHA-PQP or artesunate-mefloquine combinations.

Lumefantrine, the partner drug in AL, has a relatively short half-life (3–6 d [48]) compared to mefloquine 12–15 d [49], amodiaquine 1–3 wk [50], or sulfadoxine 6–11 d [51]. Pyrimethamine and lumefantrine share a similar half-life (2–3 d [52]). Other than for chloroquine (up to 2 mo [50]) and piperaquine (23–28 d [53]), the differences in half-lives are, however, relatively small, and the advantage of a longer half-life is potentially counterbalanced by an increased risk for selection of resistant parasites, especially in areas of intense transmission [46,54].

Antimalarial drugs have the potential to suppress the relapse of hepatic dormant stages as long as plasmodial levels remain above the therapeutic threshold. However, when drug concentrations decrease or even disappear, so does the capacity of the drug to inhibit relapses. Thus, although artemether individually shows similar efficacy rates to artesunate [38], standard measures of efficacy (e.g., 28-d parasitemia cure rate) are generally lower with AL than with other ACTs because lumefantrine is cleared from the blood rather quickly, leading to potentially earlier relapses. However, relapse of vivax infection is only delayed, and not prevented, by longer-acting partner drugs since an extended half-life does not influence the viability of hypnozoites in the liver and relapse can still occur once the drug is cleared. Over longer follow-up periods, the incidence of relapse would be expected to converge regardless of which ACT was employed. It has been proposed that an accurate comparison of relapse rates in vivax malaria requires at least 2 mo of follow-up [55], which is only rarely undertaken in clinical studies.

**Efficacy of AL in P. vivax Infection**

Clinical investigations into the efficacy of antimalarial agents have been far less extensive for P. vivax than for P. falciparum, confirming its relative neglect [13]. Indeed, only a handful of clinical trials of AL in the treatment of P. vivax monoinfection have been published [34,38,56,57]. In most studies [38–68], data on AL efficacy have been derived from subpopulation analyses within larger studies of both P. falciparum and P. vivax infections.

**Clinical Response**

AL is highly effective against the blood stages of P. vivax infection, consistent with results from trials of AL in falciparum malaria [42,69,70]. The most informative indicator of efficacy is parasitological cure, since the clinical failure rate excludes asymptomatic parasitological failures that are detected only at routine follow-up visits. Nevertheless, it is important to note that fever resolution is rapid following AL therapy [38,56,57,59].

Parasite clearance [38,56,57] is achieved rapidly in vivax-infected patients. This is not unexpected, since in vitro data have shown similar efficacy for artemether versus asexual forms of P. falciparum and P. vivax [44]. Reports from subpopulations with vivax monoinfection [38,56,57,59] or mixed vivax and falciparum infection [57,59,60,63,67] have shown rapid clearance of both species’ parasitemia in all patients following AL treatment (Table 1). In a cohort of 33 children with vivax monoinfection, mean time to parasite clearance following AL treatment was 33.6 h, with all patients being fully cleared of their parasites by day 7 [59].

**Comparison with Chloroquine and Other Antimalarials**

One randomized trial compared the therapeutic response against vivax monoinfection of different orally administered antimalarials in a Thai population of 207 patients [38]. The rate of parasite clearance was markedly faster with artemether and artesunate than with the other non-ACT antimalarials (Table 1). When the baseline parasite count was taken into consideration, by calculating the ratio of the parasite count before treatment to the count at 48 h (“parasite reduction rate”), clearance rates were higher with artemether (median 1,720), with values 14-fold greater than for the other treatments, with the exception of artesunate (median 1,507). Correspondingly, the mean fever clearance time (defined as the time for body temperature to fall below 37.5°C and remain below this value for >48 h) was fastest in patients treated with artemether or artesunate compared to other antimalarials in this study [38], consistent with results from a randomized trial in Indonesia [56] (Table 1). Other authors have reported a similar time to resolution of fever with AL or chloroquine-primaquine [56].

**P. vivax Relapse**

**Comparison with Chloroquine**

As discussed above, the relatively short lumefantrine half-life often implies a lower day 28 uncorrected parasitological cure rate with AL than with antimalarials that have a longer half-life, including chloroquine and chloroquine-primaquine [34,71]. In a recent study of AL versus chloroquine monotherapy in 133 patients with vivax malaria in Ethiopia, the uncorrected day 28 failure rate for AL was 19.0% (95% CI 2.9%–18.9%), compared to 7.5% for chloroquine (95% CI 11%–31.6%) [34] (Table 2). This difference would be expected in view of the relatively long half-life of chloroquine [50]. Resistance to chloroquine and subtherapeutic drug levels could explain the five recrudescences observed in the chloroquine group, but amongst the 19 cases of treatment failure in AL-treated patients [34], it is not possible to differentiate between relapse, recrudescence, or reinfection. One could speculate that most new parasitemias probably derived from
relapse rather than recrudescence, since all but one treatment failure occurred during days 21–28; new infections were also possible, but unlikely because of the low transmission intensity in the area. The authors also suggested that since the evening doses of AL were unsupervised, full compliance could not be confirmed, although good compliance with the AL dosing regimen has generally been observed [72,73].

The longest follow-up data comparing AL (without primaquine) to chloroquine-primaquine derive from a study in 132 Chinese patients with vivax malaria [56]. While initial parasite clearance was significantly faster with AL than with chloroquine-primaquine (33.5 h versus 44.9 h, p<0.01), cumulative relapse rates 9 mo after the initial infection were significantly higher in the two AL dosing groups (84.9% and 78.8% versus 22.9% in patients treated with chloroquine-primaquine, p<0.01). This is as expected, since radical cure requires concomitant administration of primaquine.

Only one trial has evaluated the efficacy of AL versus chloroquine when both are administered in combination with primaquine in the treatment of P. vivax malaria [57]. In this study, 98 non-G6PD-deficient adult patients with vivax malaria in Thailand were randomized to AL or chloroquine, both administered with primaquine. Mean time to parasite clearance was shorter in the AL-primaquine group (41.6 h versus 55.8 h, p<0.01), and all but one of the 47 AL patients achieved parasitological cure by day 28 (97.4%). For the remaining patient, in whom parasitemia was detected at day 26, de novo reinfection was excluded since the patient had remained in hospital; relapse was considered the most likely cause. All patients receiving chloroquine-primaquine achieved parasitological cure. The authors concluded that AL with primaquine was as effective as chloroquine with primaquine for the treatment of vivax malaria [57]. It is clear that more studies are needed to specifically investigate the combined efficacy and potential toxicity of AL and primaquine. To date, however, there has been no indication of safety or toxicity concerns in patients treated for vivax infection with AL alone [34,38,57,62] or in the single study of AL in combination with primaquine [57]. The absence of an effect of artemether on the metabolism of primaquine [74] and the absence of an inhibitory or induction effect of lumefantrine on the CYP enzymes involved in the metabolism of primaquine (i.e., CYP1A2 and CYP3A4 [75]) suggest that a drug–drug interaction between the two drugs is unlikely.

### Comparison with Other ACTs

Studies comparing the efficacy of artemisinin monotherapies to treat vivax malaria are scarce and no longer considered ethical. In

### Table 1. Parasite and fever clearance times in patients treated with artemether or AL for P. vivax.

| Study                        | Population (Location) | Treatment                  | Sample Size | Parasite Clearance Time | Fever Clearance Time |
|------------------------------|-----------------------|----------------------------|-------------|-------------------------|----------------------|
|                              |                       |                            |             | Mean Time (Hours) | p-Value | Mean Time (Hours) | p-Value |
| Karunajeewa et al. [59]       | Children 0.5–5 y (Papua New Guinea) | AL | 33 | 33.6 | <0.001 | 50.4 | 0.94 |
|                              |                       | Chloroquine-sulfadoxine-pyrimethamine | 51 | 74.4 | 55.2 |
|                              |                       | Artesunate-sulfadoxine-pyrimethamine | 39 | 26.4 | 50.4 |
|                              |                       | DHA-PQP | 38 | 28.8 | 45.6 |
| Krudsood et al. [57]          | Adults (≥15 y) (Indonesia) | AL-primaquine | 47 | 41.6 (mean; range 14–71) | <0.001 | 21.8 (mean; range 4–70) | 0.12 |
|                              |                       | Chloroquine-primaquine | 51 | 55.8 (mean; range 23–106) | 25.3 (mean; range 4–90) |
| Li et al. [56]                | Age not specified (China) | ALa | 36 | 33.5 | <0.01 | 22.3 (mean) | n.s. |
|                              |                       | Chloroquine-primaquine | 55 | 44.9 | 25.0 (mean) |
| Pukrittayakamee et al. [38]   | Adults (≥15 y) (Thailand) | Artemetherc | 20 | 50 | n.s. for artemether versus chloroquine-primaquine; p=0.02 for artemether versus artesunate | 14 | <0.001 for artemether or artesunate versus other treatments |
|                              |                       | Artesunate | 20 | 38 | 17 |
|                              |                       | Chloroquine-primaquine | 30 | 64 | 30 |
|                              |                       | Chloroquine | 30 | 65 | 31 |
|                              |                       | Primaquine | 30 | 83 | 28 |
|                              |                       | Quinine | 22 | 98 | 31 |
|                              |                       | Mefloquine | 20 | 76 | 21 |
|                              |                       | Halofantrine | 23 | 85 | 21 |
|                              |                       | Pyrimethamine-sulfadoxine | 12 | 114 | 58 |

*aStandard 3-d AL regimen.

*bData on parasite clearance time available for 195/207 patients.

*c2.7 mg/kg on day 1, 1.3 mg/kg/d for a further 4 d.

n.s., not significant.

doi:10.1371/journal.pntd.0001325.t001
the only such trial, several antimalarials were compared in a population of Thai patients. *P. vivax* relapse rates were similar for artemether (9/17 [52.9%]) and artesunate (12/19 [63.2%]) [38,71]. Parasite clearance time and fever clearance time were shortest among patients receiving artemether or artesunate compared to other non-artemisinin-based antimalarials, with no statistically significant differences between the two artemisinin derivatives [38].

Two studies have compared parasitological cure rates in vivax infection using AL or DHA-PQP: both studies showed a higher cure rate for the latter [59,62] (Table 2). A study of 161 infants and children with *P. vivax* malaria in Papua New Guinea reported a significantly higher day 28 parasitological failure rate with AL, artesunate-sulfadoxine-pyrimethamine, and chloroquine-sulfadoxine-pyrimethamine compared to DHA-PQP [59]. Ratcliff et al. [62] also observed a higher failure rate with AL versus DHA-PQP, this time in an Indonesian population [62].

### Prevention of De Novo Vivax Infection

Different studies have assessed the appearance of de novo vivax infections in patients treated with AL for falciparum malaria. A recent meta-analysis confirms the superiority of both DHA-PQP and artesunate-mefloquine to AL in reducing the incidence (reappearance or new infection) of *P. vivax* over 42 d [39], but in view of the

| Study                              | Population (Location) | Follow-Up | Treatment                  | Sample Size | Parasitological Failure | p-Value |
|------------------------------------|-----------------------|-----------|----------------------------|-------------|-------------------------|---------|
| Yohannes et al. [34]               | Adults and children ≥1 y (Ethiopia) | 28 d      | AL                         | 75          | 19%                     | 0.015   |
|                                    |                       |           | Chloroquine                | 87          | 7.5%                    |         |
| Li et al. [56]                     | Age not specified (China) | 9 mo      | AL                         | 36          | 84.9%*                  | <0.01   |
|                                    |                       |           | Chloroquine-primaquine     | 55          | 22.9%*                  |         |
| Pukrittayakamee et al. [71]        | Adults (≥15 y) (Thailand) | 28 d      | Artemetherb                | 20          | 52.9%e                  | —       |
|                                    |                       |           | Artesunate                 | 20          | 63.2%e                  |         |
|                                    |                       |           | Chloroquine-primaquine     | 26          | 0%                      |         |
|                                    |                       |           | Chloroquine                 | 49          | 0%                      |         |
|                                    |                       |           | Primaquine                 | 30          | 11.5%e                  |         |
|                                    |                       |           | Quinine                    | 22          | 64.7%e                  |         |
|                                    |                       |           | Mefloquine                 | 16          | 0%                      |         |
|                                    |                       |           | Halofantrine               | 23          | 52.9%e                  |         |
| Karunajeewa et al. [59]            | Children 0.5–5 y (Papua New Guinea) | 28 d<sup>d</sup> | AL                         | 33          | 45.5%                   | 0.001 for AL versus DHA-PQP |
|                                    |                       |           | Chloroquine-sulfadoxine-pyrimethamine | 51          | 41.2%                  |         |
|                                    |                       |           | Artesunate-sulfadoxine-pyrimethamine | 39          | 46.2%                  |         |
|                                    |                       |           | DHA-PQP                    | 38          | 15.8%                   |         |
| Ratcliff et al. [62]               | Adults and children ≥10 kg (Indonesia) | 42 d      | AL                         | 141         | 57%                    | <0.001  |
|                                    |                       |           | DHA-PQP                    | 147         | 14%                     |         |

<sup>a</sup>Relapse rate.<br>
<sup>b</sup>2.7 mg/kg on day 1, 1.3 mg/kg/d for a further 4 d.<br>
<sup>c</sup>Subsequent appearance of malaria.<br>
<sup>d</sup>Parasitological failure at 42 d: AL 54.5%, chloroquine-sulfadoxine-pyrimethamine 65.3%, artesunate-sulfadoxine-pyrimethamine 48.7%, DHA-PQP 27.8% (*p* = 0.001 versus AL).
limited difference in the duration of partner drug half-lives, this may not be sustained in the long term. In areas of intense vivax transmission that have only limited use of primaquine, however, prevention of de novo vivax infections may be achieved more effectively by ACTs in which there is an extended partner half-life.

Gametocidal Effect

Unlike in P. falciparum, where gametocytogenesis is delayed until the appearance of clinical symptoms, P. vivax generates gametocytes at an early stage of the infection, often present in vivax infections [62,71]. As a result, vivax can be transmitted to other individuals before patients have started any treatment, a circumstance which is further aggravated by the fact that P. vivax achieves effective transmission at low blood densities.

In P. falciparum infections, most antimalarial agents other than ACTs have little or no effect on gametocyte development [77–79]. However, all antimalarial agents are considered effective against both the asexual and sexual stages of P. vivax malaria [71]. Few prospective studies, however, have compared the gametocytocidal activity of different therapies against vivax, and so adequate in vitro models exist. The limited data available, however, suggest that artesiminin derivatives such as AL clear P. vivax in vitro models exist. The limited data available, however, suggest activity of different therapies against vivax, and no adequate in prospective studies, however, have compared the gametocytocidal activity of different therapies against vivax, and no adequate in vivo models exist. The limited data available, however, suggest that artesiminin derivatives against vivax infection, in a cohort of 284 Indonesian patients with P. vivax monoinfection or mixed infection [62]. In total, 56% showed vivax gametocytes on admission. The prevalence of gametocytemia remained markedly lower with both AL and DHA-PQP during the 42-d follow-up. After day 14, vivax gametocytemia seemed to increase among AL-treated patients but declined again by day 42, while for DHA-PQP-treated patients, gametocytes did not reappear until day 28 and then began a modest growth towards the end of follow-up (the gametocyte carriage rate was 24.6 and 3.7 per 1,000 patient-weeks to day 42, respectively, 0.0001). Assuming that gametocytes show a similar sensitivity to all artemisinin derivatives, these findings would be consistent with the hypothesis that the effect of ACTs on vivax gametocytogenesis is influenced by the half-life of the partner drug, capable of inhibiting relapses (and hence new gametocytes) or new infections, but with possibly no direct effect on existing gametocytes.

To our knowledge, no data are available regarding the specific impact of AL on the viability of gametocytes, an essential component for malaria transmission, which is, indeed, more critical than the absolute presence or absence of gametocytes.

Conclusions

The large burden and wide geographical distribution of P. vivax, and its clear recognition as a non-benign infection, calls for a paradigm change in the way we consider this infection. Effective treatment should be used rationally and rapidly, and although vivax may still be sensitive in many areas of the world to chloroquine, we need to acknowledge the new role that artemisinin derivatives, in combination with primaquine, will have to play in the short term for its control. AL is now widely
deployed for the treatment of falciparum malaria, based on extensive evidence of consistently high efficacy and an extensive, convincing safety data base. Clinical trials in vivax malaria are scarcer. The available data show that AL offers good efficacy against the blood stages of P. vivax seems clear, showing rapid parasite and fever clearance. The relatively short half-life of lumefantrine means that day 28 parasitological cure rates are lower for AL than for other ACTs. This probably implies a shorter time to spontaneous relapse caused by maturation of dormant hypnozoites, and the possibility of an earlier susceptibility to new infections, rather than a genuine difference in efficacy against the blood stages of vivax infection. Differences between AL and other ACTs are likely to be restricted to variations in different partner drug half-lives, which may be of limited clinical relevance especially if these drugs are given in combination with primaquine, and should be balanced against the possible risk of drug resistance, which is associated with increasingly long drug half-lives.

AL for treatment of vivax malaria may be appropriate in chloroquine-resistant P. vivax, and in co-endemic areas where AL is already used against P. falciparum, as well as when parasitological differentiation is not routinely performed and treatment is primarily based on clinical suspicion.

Key Learning Points

- The underestimation of P. vivax’s real burden and potential to cause severe disease, and the identification of increasing parasite resistance in many areas of the world to chloroquine, the mainstay of its treatment, compel the malaria community to actively search for new and effective treatment strategies.
- A unified treatment strategy for both falciparum and vivax infections using ACTs that have already been deployed in many malaria-endemic areas of the world would offer important logistical and cost advantages, especially in areas of high chloroquine resistance or where parasitological diagnosis remains challenging.
- The efficacy of AL against the blood stages of P. vivax is increasingly long drug half-lives.
- AL for treatment of vivax malaria may be appropriate in chloroquine-resistant P. vivax, and in co-endemic areas where AL is already used against P. falciparum, as well as when parasitological differentiation is not routinely performed and treatment is primarily based on clinical suspicion.

Key Papers

- Maguire JD, Baird JK (2010) The ‘non-falciparum’ malarials: the roles of epidemiology, parasite biology, clinical syndromes, complications and diagnostic rigour in guiding therapeutic strategies. Ann Trop Med Parasitol 104: 283–301.
- Pukrittayakamee S, Chantra A, Simpson JA, Vanijanonta S, Clemens R, et al. (2000) Therapeutic responses to different antimalarial drugs in vivax malaria. Antimicrob Agents Chemother 44: 1680–1685.
- Ratcliff A, Siwanantoro H, Kenangalem E, Maristela R, Wuwung RM, et al. (2007) Two fixed-dose artemisinin combinations for drug-resistant falciparum and vivax malaria in Papua, Indonesia: an open-label randomised comparison. Lancet 369: 757–765.
- Smithuis F, Kyaw MK, Phe O, Win T, Aung PP, et al. (2010) Effectiveness of five artemisinin combination regimens with or without primaquine in uncomplicated falciparum malaria: an open-label randomised trial. Lancet Infect Dis 10: 673–681.
- Douglas NM, Anstey NM, Angus BJ, Nosten F, Price RN (2010) Artemisinin combination therapy for vivax malaria. Lancet 10: 405–416.

trials are required. As with other treatments for vivax malaria, primaquine therapy should be administered in combination with AL when used to treat P. vivax infections, preferably after ascertainment of G6PD status. In areas of high transmission, or when G6PD deficiency cannot be easily excluded and primaquine use is erratic, other ACT combinations in which the half-life of the partner drug is longer (e.g., DHA-PQP) may be more efficacious to prevent relapses. However, the use of AL remains a valid alternative, and a pragmatic choice. Finally, AL and other artemisinin derivatives quickly clear P. vivax gametocytes [71,82], but the benefit in terms of reducing transmission rate is muted by the high rate of gametocyte carriage that is typical in vivax infections [62,71,76].

A unified treatment strategy for the asexual forms of both falciparum and vivax infections would offer important logistical advantages. However, the incomplete nature of current data on the efficacy of AL, and of ACTs in general, in the treatment of P. vivax mono-infections and/or the prevention of P. vivax relapses or new infections compels the malaria community to assess urgently the efficacy, cost-effectiveness, safety, and toxicity of these drugs on their own and in association with effective antihypnozoite treatment.

References

1. Guerra C, Howes RE, Pattil AP, Gotting PW, Van Boeckel TP, et al. (2010) The international limits and population at risk of Plasmodium vivax transmission in 2009. PLoS Negl Trop Dis 4: e774. doi:10.1371/journal. pntd.0000774.
2. Mendis K, Sina BJ, Marchesini P, Carter R (2003) The neglected burden of Plasmodium vivax malaria. Am J Trop Med Hyg 64: 97–106.
3. Mueller I, Galinski MR, Baird JK, Carlton JM, Kochar DK, et al. (2009) Key gaps in the knowledge of Plasmodium vivax, a neglected human malaria parasite. Lancet Infect Dis 9: 555–566.
4. Nigatu W, Abebe M, Dejene A (1992) Plasmodium vivax and P. falciparum infection, providing rapid clearance of both parasites [38,56,57] and fever [56,57]. Although ACTs such as AL, in which the partner drug has a relatively short clearance of both parasites [38,56,57] and fever [56,57]. Although AL for treatment of vivax malaria may be appropriate in chloroquine-resistant P. vivax, and in co-endemic areas where AL is already used against P. falciparum, as well as when parasitological differentiation is not routinely performed and treatment is primarily based on clinical suspicion.

5. Culleton R, Ndounga M, Zeyrek FY, Coban C, Casmiro PN, et al. (2009) Evidence for the transmission of Plasmodium vivax in the Republic of the Congo, West Central Africa. J Infect Dis 200: 1465–1469.
6. Miller LH, Mason SJ, Clyde DF, McGinniss MH (1976) The resistance factor to chloroquine and P. vivax malaria: an open-label randomised trial. Lancet Infect Dis 10: 673–681.
7. Rosenberg R (2007) Plasmodium vivax in Africa: hidden in plain sight? Trends Parasitol 23: 193–196.
23. Alvarez G, Pinares JG, Tobón A, Ríos A, Maestre A, et al. (2006) Efficacy of
20. World Health Organization (2010) WHO guidelines for the treatment of
18. Douglas NM, Anstey NM, Angus BJ, Nosten F, Price RN (2010) Artemisinin
17. Genton B, D’Acremont V, Rare L, Baea K, Reeder JC, et al. (2008) Plasmodium
15. Kochar DK, Saxena V, Singh N, Kochar SK, Kumar SV, et al. (2005)
14. Maguire JD, Baird JK (2010) The ‘non-falciparum’ malarias: the roles of
36. Teka H, Petros B, Yamuah L, Tesfaye G, Elhassan I, et al. (2008) Chloroquine-
uncomplicated falciparum malaria: an open-label randomised trial. Lancet Infect Dis 10: 673–681.

65. Thapa S, Hollander J, Linhan M, Cox-Singh J, Bista MB, et al. (2007) Comparison of artemether-lumefantrine with sulfadoxine-pyrimethamine for the treatment of uncomplicated falciparum malaria in eastern Nepal. Am J Trop Med Hyg 77: 425–430.

66. van den Broek IV, Maung UA, Peters A, Liem L, Kamal M, et al. (2005) Efficacy of chloroquine-sulfadoxine-pyrimethamine, mefloquine-artesunate and artemether-lumefantrine combination therapies to treat Plasmodium falciparum malaria in the Chittagong Hill Tracts, Bangladesh. Trans R Soc Trop Med Hyg 99: 727–735.

67. Van Vugt M, Wilaipatana P, Gemperli B, Gathmann I, Phaipun L, et al. (1999) Efficacy of six doses of artemether-lumefantrine hrendemofol in multidrug-resistant Plasmodium falciparum malaria. Am J Trop Med Hyg 60: 936–942.

68. Karbwang J, Na-Bangchang K, Thanavibul A, Mull R, Gathmann I (2000) Dose-finding study of the efficacy of fixed-combination artemether/lumefantrine for the treatment of multidrug-resistant Plasmodium falciparum malaria in Thailand. Clin Drug Invest 19: 343–348.

69. Makanga M, Krudsood S (2009) The clinical efficacy of artemether/ lumefantrine (Coartem). Malar J 8(Suppl 1): S5.

70. Mueller EA, van Vugt M, Kirsch W, Andriano K, Hunt P, et al. (2006) Efficacy and safety of the six-dose regimen of artemether-lumefantrine for treatment of uncomplicated Plasmodium falciparum malaria in adolescents and adults: a pooled analysis of individual patient data from randomized clinical trials. Acta Trop 100: 41–53.

71. Pukrittayakamee S, Chotivanich K, Clemens R, Looareesuwan S, et al. (2004) Activities of artesunate and primaquine against asexual- and sexual-stage parasites in falciparum malaria. Antimicrob Agents Chemother 48: 1329–1334.

72. Zongo I, Dorsey G, Rouamba N, Dokomajilar C, Séré Y, et al. (2007) Randomized comparison of amodiaquine plus sulfadoxine-pyrimethamine, artemether-lumefantrine, and dihydroartemisinin-piperaquine for treatment of uncomplicated Plasmodium falciparum malaria in western Kenya. Malar J 7: 237.

73. Li XQ, Bjerkman A, Anderson TB, Gustafsson LL, Masimirembwa CM (2003) Identification of human cytochrome P450s that metabolise anti-parasitic drugs and predictions of in vivo drug hepatic clearance from in vitro data. Eur J Clin Pharmacol 59: 429–442.

74. McKenzie FE, Wongrichanalai C, Magill AJ, Forney JR, Permanjah B, et al. (2006) Gametocytemia in Plasmodium vivax and Plasmodium falciparum infections. J Parasitol 92: 1281–1285.

75. Li XQ, Bjerkman A, Anderson TB, Gustafsson LL, Masimirembwa CM (2003) Identification of human cytochrome P450s that metabolise anti-parasitic drugs and predictions of in vivo drug hepatic clearance from in vitro data. Eur J Clin Pharmacol 59: 429–442.

76. McKenzie FE, Wongrichanalai C, Magill AJ, Forney JR, Permanjah B, et al. (2006) Gametocytemia in Plasmodium vivax and Plasmodium falciparum infections. J Parasitol 92: 1281–1285.