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Lancet Infect Dis. Author manuscript; available in PMC 2012 May 14.

Published in final edited form as:
Lancet Infect Dis. 2010 June ; 10(6): 405–416. doi:10.1016/S1473-3099(10)70079-7.

Artemisinin combination therapy for vivax malaria?

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Abstract

Early parasitological diagnosis and treatment with artemisinin-based combination therapies (ACT) are seen as key components of global malaria elimination programmes. In general, use of ACTs has been limited to patients with falciparum malaria whereas blood-stage *P. vivax* infections are mostly still treated with chloroquine. We review the evidence for the relative benefits and disadvantages of the existing 'separate' treatment approach versus a 'unified' ACT-based strategy for treating *P. falciparum* and *P. vivax* infections in regions where both species are endemic (co-endemic). The 'separate' treatment scenario is justifiable where *P. vivax* remains sensitive to chloroquine and providing that diagnostic tests reliably distinguish *P. vivax* from *P. falciparum*. However, with the high frequency of misdiagnosis in routine practice and the rise and spread of chloroquine-resistant *P. vivax*, there may be a compelling rationale for a unified ACT-based strategy for vivax and falciparum malaria in all co-endemic areas. Analyses of the cost-effectiveness of ACTs for both *Plasmodium* species are required to assess the role of these drugs in vivax malaria control and elimination efforts.

Introduction

Calls for the global elimination of malaria and availability of new funding sources have reinvigorated malaria control programmes. A central theme for these programmes is the development of infrastructure and treatment policy that ensures that all patients with malaria are rapidly diagnosed and have access to highly effective antimalarial drugs. Artemisinin-based combination therapies (ACT) effect rapid and sustained parasitological cure in patients with *Plasmodium falciparum* malaria[1] and have been shown to reduce transmission of this species in areas with moderate and low endemicity.[2-6] If ACTs can also fulfil their promise of delaying the emergence of further antimalarial resistance,[2,5] these effects are likely to be sustained at least in the medium term. Consequently, by 2009, 81 malarious countries had adopted ACTs for first-line treatment of uncomplicated falciparum infection.[7]

Outside of Africa, *P. falciparum* almost invariably co-exists with other human *Plasmodium* species. Of these, *Plasmodium vivax* is the most important and is currently endemic in approximately 50 countries; collectively accounting for half the world's malaria.[7-9] While vivax malaria is less frequently severe than falciparum malaria, it has been associated with

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Conflicts of Interest None declared

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death[10-13] and causes substantial morbidity and socioeconomic disruption in endemic regions.[12,14-18] According to the most recent estimates, 2.6 billion people live at risk of vivax malaria[9] of whom between 70 and 391 million become infected each year.[8,14,19] The corresponding figures for *P. falciparum* are 2.4 billion people at risk [20] and 175-630 million infections per year.[8,21]

The use of ACTs for first-line treatment of vivax malaria has received comparatively little attention, probably because this is seen as "an expensive and inefficient approach to treating a disease which can be readily treated in most cases with chloroquine."[22] By 2009, only the Solomon Islands, Vanuatu, Papua New Guinea (PNG) and Papua, Indonesia had adopted a unified ACT-based treatment policy for malaria of any cause.[7] Although laudably targeted, the resultant 'separate' treatment scenario for falciparum and vivax malaria in the other co-endemic nations has disadvantages, all of which could potentially hamper global malaria elimination efforts. This review explores the effectiveness of ACTs for vivax malaria and canvasses the relative benefits and disadvantages of the existing 'separate' treatment approach versus a 'unified' ACT-based strategy for treating both *P. falciparum* and *P. vivax* infections in co-endemic countries.

Vivax malaria

Epidemiology

Around the world, the proportion of malaria cases attributable to *P. vivax* inversely correlates with the overall endemicity of malaria.[19,23] In tropical Africa, where entomological inoculation rates (EIR) are high, *P. falciparum* predominates; a probable consequence of selection for hosts lacking the Duffy antigen used by *P. vivax* merozoites to invade red blood cells.[23,24] In contrast, where conditions are more hostile to *Plasmodium* spp. and EIRs are low (for example much of Latin America, the eastern Mediterranean, the middle East and the Korean Peninsula), *P. vivax* accounts for 50-100% of infections.[23] Globally, most *P. vivax* infections occur in the highly populated countries of southern Asia and the western Pacific where EIRs are intermediate and attributable fractions range from 40-70%.[14,19,23]

Plasmodium vivax is responsible for substantial morbidity through its propensity to cause recurrent infections associated with fever, anaemia[14,15,25] and adverse pregnancy outcomes.[13,16,17,26] It has also been associated with severe disease and death.[10-13,27-31] In southern Papua, an area of high-grade *P. vivax* chloroquine resistance, the fatality of hospitalised patients with vivax malaria is reportedly comparable to that of patients with falciparum malaria.[12,13] Elsewhere in Asia and south America, the severity of vivax malaria pales when compared with *P. falciparum* infections.[10,11]

In most co-endemic areas, morbidity associated with vivax malaria peaks at a younger age than for falciparum malaria,[32-36] a phenomenon that Maitland and colleagues postulate is due to greater ease of transmission and more rapid acquisition of immunity.[37] In these settings, older children and adults with vivax malaria are more likely to be asymptomatic than their falciparum-infected counterparts.[32,38] This inherently limits the comparative transmission-blocking potential of interventions aimed at effective treatment of symptomatic disease.

Studies from Thailand,[39,40] Papua, Indonesia[41] and Papua New Guinea[42] have shown very high rates of *P. vivax* parasitaemia following treatment for *P. falciparum* infection. Indeed in many sites, the force of these recurrences rivals that of *P. falciparum* infection in hyperendemic regions of Africa. The reasons for this are not clear. One postulate is that there is a high incidence of co-infection and that concurrent *P. falciparum* acutely suppresses

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P. vivax parasitaemia.[40] An alternative, and possibly complementary, explanation is that *P. falciparum* infection and its treatment may somehow activate dormant hypnozoites leading to *P. vivax* relapse. Irrespective of the cause, the pharmacokinetic profile of the drug used to treat *P. falciparum* can have a major impact on the rate of subsequent vivax malaria with longer half-life drugs tending to result in lower rates of recurrence, at least until 42 days.[40-42]

Biological considerations

Plasmodium vivax has a number of biological characteristics that make it comparatively refractory to the transmission-blocking effects of blood-stage antimalarials. During a primary infection, a proportion of *P. vivax* parasites will become dormant in the liver giving rise to the potential for multiple subsequent blood-stage relapses. The timing of relapses varies widely by geographic location, occurring as frequently as three-weekly in equatorial regions[40,43-45] and often greater than 6-monthly in temperate climes.[46] These relapses help to ensure transmission of the parasite, even in seasonal environments that are hostile to mosquito vectors for much of the year. It remains unclear whether the total number of relapses is predetermined or adaptive – an important distinction that partially determines the utility of long-acting schizontocidal antimalarials that can suppress the first, but not subsequent relapses.

The only licensed hypnozoiticidal agent that can reliably prevent relapses is primaquine,[47] a drug that, according to the World Health Organization (WHO), is contraindicated in those patients at greatest risk: pregnant women and infants.[48] Primaquine causes gastrointestinal side effects and can result in severe haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Moreover, adherence to the standard 14-day course is thought to be poor.[49] Rationalisation of the use of primaquine and discovery of more effective and safe hypnozoiticidal alternatives are clearly critically important goals for *P. vivax* elimination.

Mature, infective *Plasmodium vivax* gametocytes appear much earlier in the course of primary or recrudescent infections than *P. falciparum* gametocytes[19,50] with approximately 50-80%[41,51] versus 10-40%[52] of patients having patent gametocytaemia on presentation respectively. It follows that *P. vivax* is much more likely to be transmitted before treatment can be commenced.

Plasmodium vivax gametocytes are also more efficiently transmitted to mosquitoes than *P. falciparum*[53,54] and once ingested, develop into sporozoites faster than any of the other human *Plasmodium* species. [55] Ostensibly, this would suggest that insecticide treated bednets are highly appropriate means of targeting *P. vivax* transmission and indeed this has been shown to be the case in some countries.[56] However in other areas, particularly those with unstable *P. vivax* transmission, studies have shown ITNs to be a relatively poor control mechanism for this species,[56,57] possibly because of the greater propensity for vectors of *P. vivax* to bite during daytime hours.[57]

Artemisinin-based combination therapies

Artemisinin was first isolated from *Artemisia annua* in 1972.[58] Its use has now been superseded by other derivatives (notably the water-soluble hemisuccinate artesunate, the lipophilic ester artemether and dihydroartemisinin, their common metabolite). The artemisinin derivatives induce the greatest reduction in parasitaemia per asexual cycle of any of the widely available antimalarials.[59] However, because they are rapidly eliminated, their use as monotherapy is associated with high rates of recrudescence unless 7 or more days of therapy is administered to cover 3-4 asexual cycles.[60-62] Combining the artemisinins with

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partner drugs that have longer half-lives and different mechanisms of action provides protection against subsequent recrudescence and limits the development of drug resistance.[63-65] Over the last decade the role of artemisinin combination therapy (ACT) has been extensively debated and subsequently endorsed by the WHO as a central component of antimalarial treatment policy. By 2009, 81 countries had changed policy to ACT for uncomplicated falciparum malaria. The most common combinations selected were: artemether-lumefantrine (AL, n=50), artesunate-amodiaquine (AA, n=23), artesunate-sulfadoxine/pyrimethamine (ASP, n=12) and artesunate-mefloquine (AM, n=8)[7] (note: total exceeds 81 since some countries use more than one ACT). Four countries have adopted ACTs for the treatment of vivax malaria. The Solomon Islands, Vanuatu and PNG have opted for AL nationwide and Indonesia has adopted dihydroartemisinin-piperaquine (DHP) in Papua only.[21]

The pharmacokinetic and pharmacodynamic properties of the partner drugs have important implications for the effectiveness and post-treatment prophylaxis provided by the ACTs. Chloroquine and piperaquine have the longest terminal elimination half-lives (1-2 months[66] and 23-28 days respectively[67,68]), followed by amodiaquine (1-3 weeks[66]), mefloquine (~12 days[69]), sulfadoxine (6.7 days[70]), pyrimethamine (3.2 days[70]) and lumefantrine (3.2 days[71]). Of these partner drugs, chloroquine has the greatest intrinsic activity against *P. vivax* and sulfadoxine the lowest.[59,72]

Artemisinin-based combination therapies for treating *P. vivax* malaria

In areas where *P. vivax* is known to be chloroquine-sensitive, the WHO recommends three days of chloroquine plus two weeks of primaquine (provided the affected individual is not severely G6PD deficient). Where ACT has been adopted for treatment of falciparum malaria and / or in areas where *P. vivax* is known to be resistant to chloroquine, ACT plus primaquine is seen as an “appropriate” alternative, with the exception of artesunate plus sulfadoxine-pyrimethamine which is regarded as ineffective against *P. vivax* in most areas.[73]

Parasitological response

All of the artemisinins and most of the commonly used partner drugs are known to be active against asexual stages of *P. vivax.*[74] Comparing the overall efficacy of these drugs *in vivo*, however, is challenging since it is currently impossible to determine whether recurrent parasitaemia is due to recrudescence, reinfection or relapse.[75,76] The rapidity of parasite and fever clearance is indicative of the intrinsic activity of the artemisinins against *P. vivax* but does not necessarily correlate with the subsequent risk of recrudescence. Since hypnozoites are resistant to all but the 8-aminoquinoline antimalarials, the occurrence of early relapses is predominantly dependent on the elimination half-life of the partner drug rather than the level of schizontocidal activity. The cumulative risk of recurrent parasitaemia within 28-63 days of initial treatment therefore indicates the degree of post-exposure prophylaxis provided. All of these indices of treatment efficacy are dependent on pre-existing levels of parasite resistance and acquired immunity.

Our literature search revealed 11 published studies of varying design that specifically report on the efficacy or effectiveness of one or more combinations of an artemisinin derivative plus a blood schizonticide for the treatment of *P. vivax* malaria (table 1).[41,42,51,67,77-84] Ten out of 11 of these studies were from Asia and 5 were from the island of New Guinea. The most commonly investigated combinations were DHP (6 studies), AL (4 studies) and ASP (3 studies). We are also aware of further unpublished studies investigating the effectiveness of artesunate-pyronaridine[85,86] and DHP.[87]

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The studies in table 1 show a shorter time to parasite clearance in patients receiving ACTs (median parasite clearance time (PCT) = 28.8h, range 12 – 41.6h) compared to chloroquine-based monotherapy or non-ACT combination therapies (median PCT = 50.4h, range 32 – 74.4h). Only three studies reported fever clearance times for non-ACT regimens. In all cases these were longer than the corresponding times for the ACT drugs.

In support of these findings, clinical studies have shown that vivax malaria patients treated with an artemisinin derivative plus primaquine[43,88-91] or an artemisinin alone[74,92-94] have faster parasite clearance times (median PCT in these studies = 37.2h, range 14.2 – 50h) than patients treated with chloroquine ± primaquine (median PCT = 53.5h, range 24.0 – 65h). Artesunate and artemether also have significantly higher *P. vivax* parasite reduction ratios than chloroquine (844, 508 and 36 respectively).[74]

Where local parasite strains are completely sensitive, chloroquine provides good post-exposure prophylaxis against the first and possibly even second liver-stage relapse; a feature attributable to its very long terminal elimination half-life. Nevertheless the studies in table 1 show that beyond two weeks, the proportion of individuals who remained free of *P. vivax* parasitaemia after ACT treatment was at least as high, if not higher than for the individuals treated with chloroquine. This probably either reflects a degree of chloroquine resistance in the study areas or comparison with one of the longer-acting ACTs. Of the ACTs, DHP has the longest half-life and correspondingly was shown to be particularly effective at preventing *P. vivax* relapse up to as many as 56 days following initial treatment.[41,42,51] In separate studies, artesunate-mefloquine has also provided good protection against *P. vivax* parasitaemia up to 63 days following mixed[95] or *P. falciparum*[96] infections.[97] The shorter half-life combinations such as artemether-lumefantrine, although equally effective at rapidly reducing the parasite biomass, provide comparatively little cover against early relapses.

Effects on the Emergence and Spread of Parasite Resistance

Whereas chloroquine-resistant (CQR) *P. falciparum* was first documented over 50 years ago, resistant strains of *P. vivax* have taken much longer to emerge. Several factors are likely to have contributed to this disparity. Firstly, *P. vivax* gametocytes appear earlier in the course of disease and therefore are more likely to be transmitted prior to drug exposure. Secondly, a greater proportion of adults with *P. vivax* infections are likely to be asymptomatic compared with their falciparum-infected counterparts leading to less antimalarial drug usage and therefore less selective pressure for resistance-conferring mutations. And thirdly, *P. vivax* can only efficiently invade reticulocytes leading to lower total parasite biomass infections and thus a statistically smaller chance of *de novo* resistance-conferring mutations arising and being propagated.[64,65]

The first cases of CQR *P. vivax* were documented in Australian soldiers repatriated from Papua New Guinea in 1989.[98] Since then, reports of chloroquine resistance have been published from throughout the vivax-endemic world (figures 1a and 1b). Although some of this apparent spread is likely to be attributable to increased recognition and therefore greater reporting of the problem, this cannot explain the increasing degree of resistance in many places. In Papua, eastern Indonesia, the proportion of chloroquine-resistant parasites is between 64 and 84%.[99-103] Failure rates at day 28 exceeding 10% have also been reported from other parts of Indonesia,[104] Papua New Guinea,[42] India,[105] Myanmar,[106] Turkey[107] and Madagascar.[108] Elsewhere, resistance has been described but generally falls below 5%.[79,82,92,109-124] With continued use of chloroquine in these regions, the situation is likely to deteriorate.

Various ACTs have been shown to be effective against highly chloroquine-resistant strains of *P. vivax*.[41,42,81] In line with current rationale for ACTs in falciparum malaria, the

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protection afforded by combining drugs with different mechanisms of action and the very rapid reduction in parasite biomass induced by the artemisinins suggests that the ongoing effectiveness of the artemisinin component is likely to be more assured than the ongoing effectiveness of chloroquine. However empirical evidence supporting this is lacking. Conversely, long-acting partner drugs, such as piperaquine, may be comparatively prone to the development of *P. vivax* resistance since they are more likely to be present at low levels in the bloodstream at the time of the first, and possibly even second, relapse long after any therapeutic trace of the artemisinin derivative has been eliminated. Since asexual relapses are frequently associated with concurrent gametocytaemia,[41] partially resistant parasites that break through low concentrations of the partner drug will have a selective transmission advantage.

The ongoing effectiveness of the artemisinins against *P. vivax* would require their exclusive use in combination with effective partner drugs. There would also need to be sufficient monitoring in place to enable early detection of resistance and thus a timely change of partner drug before there was any threat to the artemisinin. These major operational concerns apply for the entire malarious world, not just countries with co-endemicity.

Transmission-blocking potential

Malaria is transmitted between humans by the female anopheles mosquito which must first ingest *Plasmodium* gametocytes from an infected host. Factors determining the likelihood of this event include the duration an individual has viable gametocytes in the peripheral circulation, the level of gametocytaemia and the infectiousness of the gametocytes to the local anopheline vectors. The ACTs prevent or decrease the risk of infectious *P. falciparum* gametocytaemia by rapidly reducing the biomass of precursor asexual forms, killing immature gametocytes and minimising the risk of recrudescence.[6,125] In vivax malaria, the primary means by which a chemotherapeutic agent may decrease or prevent gametocytaemia is by preventing recrudescence or liver stage relapse.

Even in regions where chloroquine retains high efficacy, treatment of *P. vivax* with an artemisinin-containing regimen results in faster reduction of gametocyte biomass. In Bangkok, the median duration of gametocytaemia in hospitalised patients treated with artesunate was significantly shorter than patients treated with chloroquine (24 hours, range 0-96 hours versus 24 hours, range 0-264 hours respectively, p=0.005).[126] However, such rapid clearance is of relatively minor transmission-blocking benefit given that gametocytes are likely to have appeared and been transmitted prior to symptom onset. Since most ACTs are eliminated faster than chloroquine, there is a theoretical potential for the shorter duration of post-exposure prophylaxis to lead to greater recurrence and associated gametocytaemia.[41] However, in Afghanistan, where *P. vivax* retains susceptibility to chloroquine, the long-acting combination DHP was associated with fewer asexual recurrences by day 63 than chloroquine, even though both regimens were associated with 100% cure at 28 days.[51] Similarly in Mae Sot, Thailand, an area of moderately high *P. vivax* chloroquine susceptibility, patients treated with DHP had half the gametocyte carriage rate of those treated with chloroquine up to 63 days of follow-up (unpublished data).

As chloroquine resistance emerges, the duration of post-exposure protection against relapse or reinfection will decline (as demonstrated in table 1) and recrudescences will become more frequent.[6,125] Introduction of ACTs for the treatment of vivax malaria in these circumstances should lead to the full range of potential transmission-blocking benefits including more rapid gametocyte clearance, fewer recrudescences and greater post-exposure prophylaxis; the latter probably only being significant for combinations with long-acting partner drugs. In southern Papua, an area with relatively high *P. vivax* transmission

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intensity, gametocyte carriage to day 42 was almost 7 fold lower in those treated with DHP compared to the shorter-acting combination artemether-lumefantrine.[41]

It should be noted however, that it is still not known whether suppressing the first relapse will reduce the total number of relapses from a particular parasite strain or will simply delay their onset. Although prophylaxis against the first relapse should provide a greater chance for haematological recovery, the effect this has on limiting transmission remains uncertain.

‘Separate’ versus Unified Treatment Approach

The artemisinin derivatives are clearly highly active against *P. vivax* and, if coupled with certain other blood schizonticides, may have advantages over chloroquine for this species. But should a unified ACT-based protocol replace the “separate” treatment approach used in most co-endemic nations? Policy-makers must weigh-up wide-ranging malariometric, operational and economic factors.

Malariometric considerations

Perhaps the greatest potential compromise associated with instituting a unified ACT-based treatment strategy is the use of a combination that is unequally effective against the different *Plasmodium* species. Artemisinin combination therapies are assumed to be effective against infections by *P. malariae* and the blood stages of *P. ovale,* though confirmatory data are sparse[127,128] and the relative advantages and disadvantages of the different combinations are unknown. The long-acting combination dihydroartemisinin-piperaquine has been shown to be particularly effective for vivax infections, inducing rapid reduction in parasitaemia and high rates of parasitological cure at 42 days.[41,42,81] Given that mefloquine and pyronaridine have long elimination half-lives and good activity against chloroquine-resistant *Plasmodium* species,[129,130] ACTs containing these antimalarials are likely to have similar pharmacodynamic advantages.

Globally, artemether-lumefantrine is the most widely used artemisinin combination for malaria and has been heavily subsidised by various international funding agencies. Although AL is a good option for falciparum malaria, it provides comparatively little post-exposure prophylaxis against *P. vivax* relapse and is thus unlikely to be the drug of choice for this species (recurrence rates for AL at day 42 in studies from Papua and PNG were 57% and 70% versus 14% and 31% for DHP).[41,42] However, if antirelapse treatment can be combined with ACTs in a reliable, safe and effective way, then the superior efficacy against *P. vivax* afforded by the longer-acting combinations would be limited to a reduction in the rate of post-exposure reinfection which, in most vivax endemic regions, is relatively low. Of course, any unified ACT-based strategy would be contingent on the continued effectiveness of these combinations for falciparum malaria – a prerequisite that now seems less assured than previously thought.[131,132]

The activity of primaquine against *P. vivax* hypnozoites is potentiated by co-administration of blood schizonticides.[133] A small study of *P. cynomolgi* in Rhesus monkeys suggested that chloroquine may be better than quinine in this regard.[134] In humans, however, chloroquine and quinine appear to be equally and highly efficacious at preventing relapse when given concurrently with primaquine for the treatment of fully drug sensitive parasites.[133] The activity of the ACTs in combination with primaquine is unknown and therefore there is a potential that their introduction for treatment of vivax malaria in conjunction with primaquine antirelapse therapy could lead to a relative reduction in relapse prevention. However, the only 8-aminoquinoline-blood schizonticide combination administered concurrently that has not shown good efficacy at preventing relapse is pentaquine plus chlorguanide, an unsurprising observation given the relatively poor activity of antifolates

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against *P. vivax*.[134] In view of the excellent blood schizonticidal activity of the artemisinins and partner drugs such as piperaquine and lumefantrine, lack of synergy with primaquine seems unlikely, but confirmatory studies are warranted.

Inflammation plays an important role in the pathogenesis of *P. vivax* infection and may be responsible for some of the manifestations of severe disease such as acute lung injury.[26,135,136] Since chloroquine has anti-inflammatory activity, it has been hypothesised that its use might ameliorate the development of these manifestations – an effect that could be lost if chloroquine was replaced by ACTs.[135]

Continued use of chloroquine rather than ACTs for the treatment of vivax malaria also has hypothetical disadvantages. Perhaps the greatest of these relates to the emergence and spread of chloroquine resistance. Diagnosis of declining drug efficacy in *P. vivax* malaria is difficult and therefore low-grade resistance often goes unnoticed. Sufficient studies have been done, however, to show that chloroquine resistance is both more widespread and severe than previously recognised (see figures 1a and b). If chloroquine remains the mainstay of treatment for vivax malaria, not only will it continue to be deployed in areas where its efficacy is declining, it is likely to gradually propagate the emergence and spread of further chloroquine resistance.

The ‘separate’ treatment approach leads to inadvertent use of chloroquine for *P. falciparum* infections. Field microscopy results in substantial mis-speciation and under-diagnosis of mixed infections.[12,137,138] On the Thai-Myanmar border, 11% of *P. vivax* monoinfections diagnosed by field microscopy were actually found to be *P. falciparum* or mixed species infections on cross-checking.[138] Furthermore, even if microscopic diagnosis of *P. vivax* is correct, subpatent co-infection with *P. falciparum* is common.[139,140] New generation rapid diagnostic tests can distinguish *P. falciparum* from *P. vivax* but the sensitivity and specificity of these tests is often poor.[141] Therefore, in routine practice in co-endemic regions, a significant proportion of patients with *P. falciparum* infections are likely to be treated with chloroquine alone. Since this drug is partially or completely ineffective against falciparum malaria in most parts of the world, its inadvertent use will result in increased transmission and morbidity from this species, as well as a greater risk of progression to severe disease or death.

Continued use of separate treatment strategies may exert unwanted selective pressure on *P. vivax* parasites, especially for drugs with long half-lives. In Thailand, use of mefloquine for falciparum malaria (either alone or in combination with artesunate) has lead to an increased prevalence of *P. vivax* isolates with *pvmdr1* amplification - a molecular marker associated with increased resistance to mefloquine.[142,143] Selection for the *pvdhfr* and *pvdhps* resistance-conferring mutations has also been observed following antifolate exposure in Thailand,[143] Papua, Indonesia[79] and Madagascar.[144] These observations highlight that use of antimalarial drugs specifically for *P. falciparum* infection may limit their future utility against *P. vivax*.

One of the major rationales for artemisinin combination therapies is their potential to delay the emergence of *de novo* parasite resistance.[64] Once resistance has emerged, however, combinations of pharmacokinetically mismatched drugs will still be vulnerable to selective transmission of resistant parasites.[145] Mathematical models have shown that simultaneously deploying multiple first-line antimalarials may retard the emergence and fixation of drug resistant *P. falciparum* by decreasing total parasite exposure to a single agent.[146] However, these models assume concurrent use of highly effective drugs and therefore would not necessarily apply to inadvertent exposure to chloroquine in areas where chloroquine

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resistance is already present. Similar multi-treatment strategies have yet to be investigated for *P. vivax*.

Operational Considerations

One of the greatest challenges for the malarious world is getting the right drugs to all of the people that need them at the right time. In most endemic areas, a high proportion of patients will seek treatment in the private or informal sector in the first instance. [38,147,148] Since diagnosis of malaria in such settings is usually based on clinical symptoms alone, it is critically important that the drugs prescribed at these facilities are effective against all local species of *Plasmodium.* Continued use of chloroquine in public health care systems could hypothetically sustain the use of chloroquine in the private sector through the legitimisation of its use and potentially also through shared supply channels.

Overall, a unified treatment strategy would be easier for health care providers to implement, would not be dependent on correct parasitological speciation and might have a greater chance of being adopted in the private sector. Drug resistance monitoring and antimalarial supply chains might be simplified and patients might develop a greater expectation of receiving the most effective drug. However, there is also a potential that a unified treatment strategy would decrease the impetus for health care providers to set up and implement parasitological testing. This might result in a greater proportion of aparasitaemic patients receiving antimalarial medications with associated implications for the development of ACT resistance, misdiagnosis of other febrile illnesses and reduced cost-effectiveness. Furthermore, since speciation is necessary for targeting primaquine therapy, it could reduce the likelihood that patients with vivax malaria receive this critically important drug.

Economic Considerations

Chloroquine is a cheap and widely available drug whereas ACTs are considerably more expensive, even with subsidy, and are limited by supply issues. Table 2 shows current estimates for the purchase price of full co-packaged adult courses of various ACTs compared with chloroquine.[149] The additional global cost associated with using DHP or AA as opposed to chloroquine for the treatment of vivax malaria can be estimated to be between 60 and 364 million US dollars per year. It must be noted that these figures do not account for any potential cost-savings associated with the use of ACTs, such as reductions in the number of recurrent *P. vivax* infections requiring retreatment, decreases in the overall incidence of vivax malaria and a reduction in the number of recrudescent, severe and fatal cases of falciparum malaria arising due to inappropriate use of chloroquine. With worsening chloroquine resistance throughout the world, these potential savings are likely to become more significant with time.

In addition to savings associated with a reduction in the burden of malaria, a unified treatment strategy would streamline antimalarial procurement and distribution systems and provide greater impetus for drug companies to reduce ACT manufacturing costs. These potential savings are unavoidably speculative since to date there have been no comprehensive cost comparisons or cost-effectiveness analyses of the use of ACTs versus chloroquine for vivax malaria.

Conclusions

Several artemisinin-based combination therapies have shown high efficacy against asexual and sexual stages of both chloroquine sensitive and resistant *P. vivax.* Where chloroquine resistance has emerged, long acting ACTs such as dihydroartemisinin-piperaquine and artesunate-mefloquine will provide greater post-exposure prophylaxis against early

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recurrence of infection. This advantage will become more pronounced as chloroquine resistance increases.

In areas of established high-grade *P. vivax* chloroquine resistance, such as across the island of New Guinea, policymakers are already implementing unified ACT-based treatment policy. In regions of low-grade resistance and where *P. vivax* retains susceptibility to chloroquine, the best treatment strategy is less obvious and the relative malariometric, operational and economic costs and benefits of ACTs versus chloroquine need to be compared. 'Separate' treatment protocols for the two species in such areas may be justifiable if diagnostic tests reliably distinguish *P. vivax* from chloroquine-resistant *P. falciparum*. However, with the relatively high frequency of misdiagnosis in routine practice and the rise of chloroquine-resistant *P. vivax*, there may be a compelling rationale for a unified ACT-based strategy for both species in all co-endemic settings. To date, consideration of the use of ACTs for vivax malaria has been stifled by the supposedly prohibitive additional expense this would imply. This view is based on assumption rather than scientific evidence and overlooks the potential malariometric advantages of ACTs, their falling cost and the operational efficiencies of a pragmatic, unified ACT-based treatment protocol. The global burden of *P. vivax* and its unique biological characteristics remain a major hurdle to the goal of malaria elimination. Studies of the cost-effectiveness of unified ACT-based strategies for malaria treatment should be prioritised to assess the role of ACTs in vivax malaria control and elimination efforts.

Search Strategy and Selection Criteria

We searched PubMed, MEDLINE, EMBASE, Global Health and the Cochrane libraries of systematic reviews and randomised controlled trials using the keywords: "vivax" and "artemisinin" or "artemether" or "arteether" or "dihydroartemisinin" or "artesunate" (expanded to all relevant MeSH headings when available) in order to determine the effectiveness of ACTs for vivax malaria and: "vivax" and "chloroquine" and "resistan$" to determine the extent of chloroquine resistance. We also searched the Australian and New Zealand, American, United Kingdom and WHO clinical trial registries, the reference lists of relevant articles and asked experts in the field for information on any other relevant published or unpublished research. In cases where articles were written in a language other than English or we were unable to obtain full text versions, we relied on information from the abstracts. We did not set date restrictions in our searches.

Acknowledgments

We would like to thank Carlos Guerra for his help with the *P. vivax* chloroquine resistance cartography. NMD received funding from the Rhodes Trust. NMA is supported by a National Health & Medical Research Council (NHMRC) Practitioner Fellowship. FN is a Wellcome Trust Senior Research Fellow.

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Current positions

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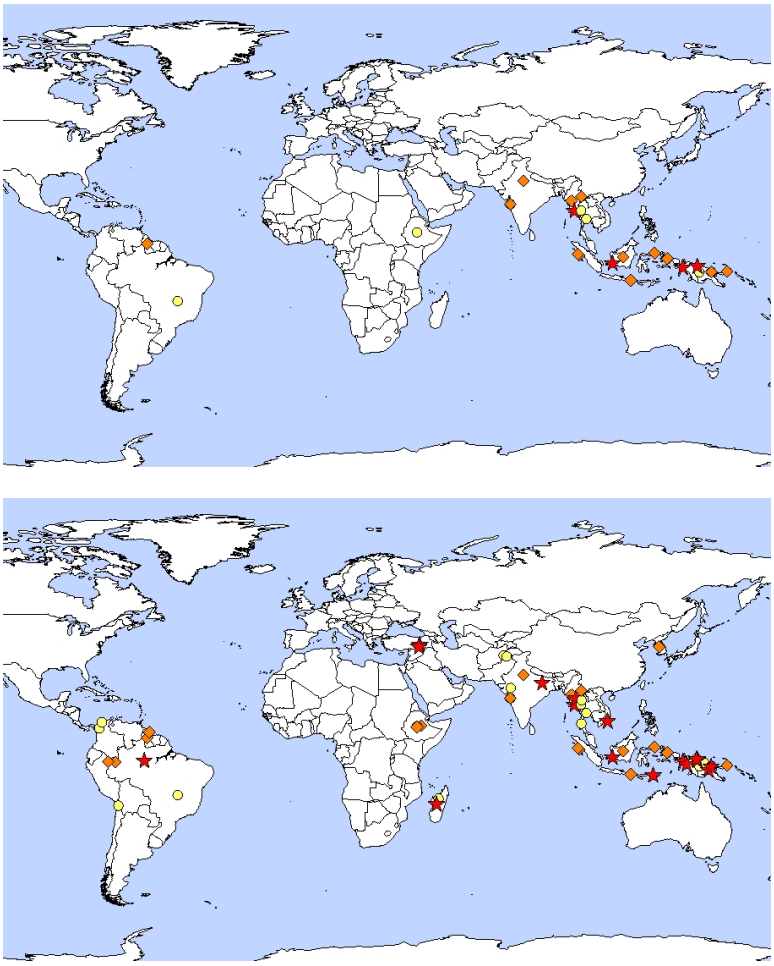

Figures 1a and 1b.

Reports of chloroquine-resistant *Plasmodium vivax* by 1999 (a) and 2009 (b). Red stars = >10% recurrence (and greater than 5 absolute failures) by day 28 with or without chloroquine levels; orange diamonds = <10% recurrence (or less than 5 absolute failures) by day 28, with chloroquine levels; yellow circles = <10% recurrence (or less than 5 absolute failures) by day 28, without chloroquine levels.

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Lancet Infect Dis. Author manuscript; available in PMC 2012 May 14.

Table 1

Studies of the effectiveness of an artemisinin derivative combined with a blood schizonticide for the treatment of *Plasmodium vivax* malaria

First Author	Year	Location	Study design	Drug (days)	N	PCT	FCT	Prop. free of recurrence			
								Day 14	Day 28	Day 42	Day 56
Li et al.[77]*	1999	China	Efficacy study, not otherwise specified	AM (3) + L (3) (higher dose)	36	33.5 h	22.3 h				
				AM (3) + L (3) (lower dose)	41	30.5 h	23.2 h				
				CQ + P†	55	44.9 h	25.0 h				
LeYuan et al.[78]*	2001	Eritrea	Efficacy study, not otherwise specified	DHA† + PY†	?	24.0 h					
				PY†	?	32.0 h					
Tjitra et al.[79]	2002	Papua, Indonesia	Non-randomised, pilot efficacy study	AS (3) + SP (1)	22	1.1 d	1.4 d	100%	89.5%		
				CQ (3) + SP (1)	6				67%		
				CQ (3)	9				11%		
Hung et al.[67] & Karunajeewa et al.[80]	2003	Cambodia	Non-randomised, population PK and safety evaluation	DHA (2) + P (2)	10	12 h			100%		
Hasugian et al.[81]	2007	Papua, Indonesia	Open-label, randomised controlled trial	DHA (3) + P (3) + PQ (14)	74					84%	
				AS (3) + AQ (3) + PQ (14)	75					52%	
Kolaczinski et al.[82]	2007	Afghanistan	Open-label, randomised controlled non-inferiority trial	AS (3) + SP (1)	94				99%	76%	
				CQ (3)	96				96%	54%	
Krudsood et al.[83]	2007	Bangkok, Thailand	Open-label, randomised controlled trial	AM (3) + L (3) + PQ (14)	47	41.6 h	21.8 h		97.4%		
				CQ (3) + PQ (14)	51	55.8 h	25.3 h		100%		
Ratcliff et al.[41]	2007	Papua, Indonesia	Open-label, randomised controlled trial	DHA (3) + P (3) + PQ (14)‡	147					86%	
				AM (3) + L (3) + PQ (14)‡	141					43%	

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First Author	Year	Location	Study design	Drug (days)	N	PCT	FCT	Prop. free of recurrence			
								Day 14	Day 28	Day 42	Day 56
Karunajeewa et al.[84]	2008	Papua New Guinea	Open-label, randomised population PK and efficacy trial	DHA (3) + P (3)	3					66.7%	
				CQ (3) + SP (3)	1¶						
Karunajeewa et al.[42]	2008	Papua New Guinea	Open-label, randomised controlled trial	AM (3) + L (3)	39	1.4 d	2.1 d		48.5%	30.3%	
				DHA (3) + P (3)	44	1.2 d	1.9 d		84.2%	69.4%	
				AS (3) + SP (1)	51	1.1 d	2.1 d		51.3%	33.3%	
				CQ (3) + SP (1)	61	3.1 d	2.3 d		51.0%	13.0%	
Awab et al.[51]	2010	Afghanistan	Open-label, randomised controlled trial	CQ (3)	268				100%		91.1%
				DHA (3) + P (3)	268				100%		97.2%

Abbreviations: PK; pharmacokinetics, DHA; dihydroartemisinin, PY; pyronaridine, AS; artesunate, SP; sulfadoxine-pyrimethamine, CQ; chloroquine, P; piperaquine, PQ; primaquine, AQ; amodiaquine, AM; artemether, L; lumefantrine, N; number, PCT; parasite clearance time, FCT; fever clearance time. *; assessment based on abstract alone, †; unknown duration, ‡; primaquine delayed until day 2, ¶; lost to follow-up. Excludes studies of artemisinin plus primaquine since the latter has no activity against asexual *P. falciparum* parasites and is therefore not an option as the sole partner drug for widespread use against both species. Studies by Ratcliff, Hasugian and Karunajeewa (2008) included patients with *P. vivax* and mixed *P. vivax/P. falciparum* infections in their analyses of *P. vivax* recurrence.

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Table 2

Costs of artemisinin-based combination therapies compared with chloroquine, 2008

Drug	Total dose for full adult course (60kg)	Minimum cost per full adult course (US$)	Additional purchase cost per course (US$)	Additional global purchase cost per year* (US$)
Artemether-lumefantrine	120mg/720mg	1.474	1.405	98-549 million
Artesunate-amodiaquine	600mg/1836mg	0.918	0.849	60-332 million
Artesunate-mefloquine	600mg/1500mg	3.85	3.781	0.26-1.5 billion
Artesunate-sulfadoxine/pyrimethamine	600mg/2000mg/100mg	1.38	1.311	92-513 million
Dihydroartemisinin-piperaquine†	135mg/1080mg	1.00	0.931	65-364 million
Chloroquine	1500mg	0.069	-	-

*Assumes: a) there are 70-435 million *P. vivax* infections per year, b) all of these infections are treated, c) adherence to World Health Organization dose recommendations and d) the average total dose administered is 2/3rds of a full adult dose

†As DHP is not yet manufactured according to International Good Manufacturing Practice standards, the cost in this table is conservatively set at one US dollar per treatment course based on a predicted public sector price of “less than one US dollar in adults and less than 0.5 US dollars in children” (Duparc, Medicines for Malaria Venture – personal communication).

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Table 3

Outstanding questions regarding the use of artemisinin-based combination therapies for vivax malaria

Is the number of *P. vivax* relapses predetermined or adaptive?
Is primaquine as effective at preventing relapses when used in combination with ACTs as when used with chloroquine?
Is there any increase in inflammatory sequelae, such as lung injury, associated with the use of ACTs for vivax malaria instead of chloroquine?
What is the additional morbidity and mortality of falciparum malaria caused by inadvertent treatment of *P. falciparum* with chloroquine due to having separate treatment strategies?
If a unified treatment strategy was seen as desirable, which artemisinin-based combination would be the most appropriate for use in co-endemic settings?
What are the operational benefits and disadvantages of a unified versus a separate treatment strategy in co-endemic regions?
What is the cost-effectiveness of using ACTs for the treatment of both vivax and falciparum malaria in co-endemic areas?

Abbreviations: ACT; artemisinin-based combination therapy