

# Malaria: Future Outlooks

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## ABSTRACT

With the emergence of multidrug-resistant falciparum malaria, new drugs and drugs in combination are urgently needed.

New antimalarial drugs investigated at the Hospital for Tropical Diseases of the Faculty of Tropical Medicine at Mahidol University in Bangkok, Thailand in recent years for treatment of uncomplicated and severe falciparum malaria are as follows: atovaquone, and artemisinin derivatives (artesunate, artemether, arteether, and dihydroartemisinin) combined with other antimalarials.

Atovaquone plus proguanil (Malarone<sup>®</sup>), artemisinin derivatives combined with lumefantrine or doxycycline, and mefloquine combined with tetracycline or doxycycline have been evaluated with improvement of the cure rate in uncomplicated malaria. Artemisinin derivatives parenterally or intrarectally combined with mefloquine may be alternatives to intravenous quinine for treatment of severe malaria.

In Thailand, drug treatment for uncomplicated malaria consists of the combinations of artesunate plus mefloquine or artemether plus lumefantrine or quinine plus tetracycline. In treatment of severe malaria, antimalarial drugs of choice are intravenous quinine or parenterally/intrarectally artemisinin derivatives plus mefloquine. (*J Infect Dis Antimicrob Agents* 2002;19:125-32.)

## INTRODUCTION

Antimalarial drug resistance has increased over the past 40 years leading to dramatic decline in the efficacy of most affordable antimalarial drugs. The resistance can be prevented, or at least delayed. Malaria must be treated adequately and selective pressures minimised. Currently recommended methods for assessing drug resistance in high-transmission areas

ignore low-grade resistance and yet this is the stage at which preventive measures are most effective, experimentally, drug resistance can be induced most efficiently by repeatedly reducing the parasite load (*in vivo* or *in vitro*) with antimalarial drug treatment that is not sufficient to eradicate the parasite load. This is what happens *in vivo* with inadequately treated malaria either as a result of inappropriate prescribing, poor

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compliance, or occasionally unusual pharmacokinetic properties of the drug. Factors that contributed to treatment failures depend upon three major elements (host, agent and drug). Complete treatment courses with adequate antimalarial doses must be given. For example, short acting drugs such as artemisinin and its derivatives or quinine need to be present at therapeutic concentrations for at least four asexual cycles (a 7-day treatment course), to ensure eradication of all the parasites. Drugs which persist for weeks or months at sub-therapeutic levels in the blood cannot offer complete protection no matter how well prescribed. In management of malaria, early diagnosis and early treatment with potent antimalarials are the fundamental components of effective strategy. If patients deteriorate they should be referred to a hospital. Correct use of an effective antimalarial drug will not only shorten the duration of malaria illness but also reduce the incidence of complications and the risk of death. New drug development is not keeping pace. Drugs are not distributed or available where they are needed, and existing drugs are not correctly used. The rational use of artemisinin derivatives in combination with long-acting drugs is now being promoted.

### NEW APPROACHES

Antimalarial drug (Table 1) development follows six approaches 1) inhibition of MSP 1 processing protease, 2) third generation antifolate malaria drug combinations, 3) *Plasmodium falciparum* fatty acid biosynthesis, 4) inhibition of malaria lactate dehydrogenase, 5) inhibition of phospholipid metabolism and 6) *P. falciparum* protein farnesyltransferase inhibitors.<sup>1,2</sup> It can take over 5 years to discover one new antimalarial drug. In contrast, antimalarial drug development (Table 2), might take a shorter period (3-5 years). This includes the development of an intravenous artemisinin (artelinate) derivative for severe malaria, the development of an artesunate/

dihydroartemisinin suppository, the development of an artesunate-sulfadoxine/pyrimethamine, artesunate-amodiaquine, an artesunate-chlorproguanil-dapsone combination, the development of a synthetic endoperoxide, the development of isoquine (4-aminoquinoline) the development of artesunate-pyronaridine in combination and artesunate/dihydroartemisinin-piperaquine.

### RATIONAL USE OF COMBINATION THERAPY

Many malaria endemic countries challenged by endemic malaria are beginning to face a situation where there are no affordable, effective antimalarial drugs. Combination therapy is used to preserve the efficacy of existing antimalarial drugs and prolong therapeutic use, although they may not necessarily provide better treatment for consumers. The development of artemisinin and its derivatives has led to several large trials aimed at assessing different combinations of existing drugs and to the specific development of new combination drugs. Several countries have also evaluate potential first-line treatments, drug combinations that do not include artemisinin. These changes have provided the impetus for the updating antimalarial treatment policies.

Antimalarial drug combinations are used to improve efficacy, and delay the development of drug-resistant parasites (Table 3). Combination therapy is standard practice in treating other diseases (tuberculosis, many cancers and HIV). Resistance is due to mutations in genes controlling the structure/activity of the therapeutic target. The chance that a mutant emerging which is simultaneously resistant to two drugs with different mechanisms of action is unlikely. Combinations that do not contain an artemisinin derivative could be a preferred option for reasons of cost and accessibility in some countries. The combination of an artemisinin derivative with a long acting antimalarial is preferred. Artemisinin will kill most of the parasites, and residual parasites will be

cleared by long acting drugs (Table 3). Although there is increased potential for toxicity, this has not proved to be a problem in practice. Combination therapy could be a viable option for countries that have widespread resistance of *P. falciparum* to chloroquine, amodiaquine, and sulfadoxine-pyrimethamine, provided that the issues of cost and the complexity of implementation can be addressed. Further data on factors affecting access to

treatment in endemic countries, including health-seeking behavior, should be explored. A system should be established to monitor antimalarial sensitivity patterns in Southeast Asia; this will require international exchanges of information. Efforts should be made to intensify resistance monitoring and to develop improved easy-to-use tools, drug sensitivity test kits and methods to facilitate this resistance monitoring.

**Table 1. Antimalarial drugs exploited since 1930.**

Old drugs	New drugs
• Cinchona alkaloids, pamaquine	• Artemisinin
• Mepacrine, chloroquine	• Artesunate, artemether, arteether
• Proguanil, amodiaquine	• Pyronaridine
• Pyrimethamine, primaquine	• Mefloquine, halofantrine
• Pyrimethamine-sulfa combinations	• Atovaquone-proguanil
• Artemether-lumefantrine	• Tafenoquine

**Table 2. Approaches to antimalarial drug development.**

• Artemisinin derivatives (e.g. artelinate)
• Artesunate-chlorproguanil-dapsone
• Synthetic endoperoxide development
• Isoquine development
• Artesunate-sulfadoxine/pyrimethamine
• Artesunate-amodiaquine
• Artesunate-pyronaridine
• Artesunate/dihydroartemisinin-piperaquine
• Artesunate/dihydroartemisinin-suppository

**Table 3. Benefits of combination of an artemisinin derivative and a long acting antimalarial.**

• Accelerate the therapeutic response
• Reduce transmission
• Prevent dangerous early treatment failures in case of high grade resistance
• Reduce the parasite load
• Reduce the chance of a resistant mutant surviving
• Long acting antimalarial will “protect” the artemisinin derivative

## NEW ANTIMALARIAL DRUG TRIALS IN THAILAND

The drug trials carried out at the Hospital for Tropical Diseases, are summarized in this paragraph (Fig. 1).<sup>3,4</sup> Atovaquone, a hydroxynaphthoquine, was evaluated and found when used alone to be safe and effective. All patients were clinically cured, but one third of patients had recrudescence (RI). When atovaquone was combined with proguanil, the cure rate increased to 100 percent.<sup>5,6</sup> This combination (a fixed-combination drug) is named Malarone<sup>®</sup>. Artemisinin derivatives such as artesunate, artemether, arteether and dihydroartemisinin have also tested. Artesunate or artemether, at a total dose of 600 to 750 mg given over 5-7 days produced cure rates of 80 to 95 percent. However, when they were combined with mefloquine (1,250 mg total dose) the cure rates increased to 95-100 percent.<sup>7-10</sup> Artesunate and dihydroartemisinin suppositories have proved successful for the treatment of severe malaria.<sup>11-14</sup> The artemisinin derivatives (600-750 mg total dose), when used in combination with mefloquine (1,250 mg total dose) over 3 days in adults gave improved cure rates (95-100%). Dihydroartemisinin alone using a total dose of 480 mg given over 5 days resulted in a cure rate of 90

percent.<sup>15,16</sup> Arteether, a WHO/TDR supported drug, has been evaluated in the hospital and now has been licensed for use in severe malaria as Artemotil<sup>®</sup>.<sup>17</sup> Other combinations (artemisinin derivatives combined with lumefantrine or doxycycline and mefloquine combined with tetracycline or doxycycline) have been evaluated also showing improvement in cure rates.<sup>18,19</sup> Recently, a fixed combination drug (artemether plus lumefantrine) named Coartem<sup>®</sup> (given as six doses in 72 hours) has proved to be a safe and effective drug for the treatment of falciparum malaria and it has been authorized for use in many western countries.<sup>20,21</sup> During the past decade, studies using combinations of artemisinin derivatives plus mefloquine (in various doses and durations of treatment) have been investigated. In general, artemisinin derivatives (12 mg/kg given over 3 days) combined with mefloquine (25 mg/kg given over 3 days) are the standard regimen for the treatment of multidrug resistant falciparum malaria in Thailand. Until proven otherwise, the above drug combinations are likely to remain the standard recommendation for treating patients suffering from acute uncomplicated falciparum malaria contracted in multidrug resistant areas.

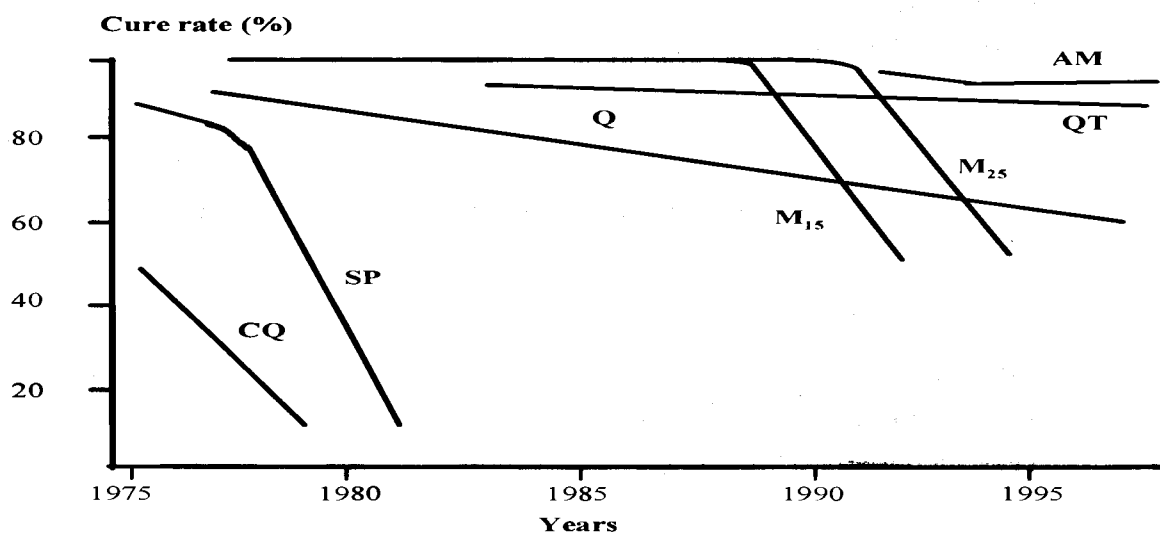


Fig 1. Efficacy of antimalarial drugs monitoring at the Bangkok Hospital for Tropical Diseases.

**Table 4. Clinical criteria for referral to a higher level of health care.**


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• Alteration in the level of consciousness
• Jaundice
• Severe anemia
• Acidotic breathing (deep laboured breathing)
• Convulsions
• Bleeding
• Black urine

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**Table 5. Management of severe malaria.**


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Pre-hospital	Awareness Preventive chemotherapy
Village level	Any effective antimalarial by any route is better than nothing. Rectal formulations of artemisinin are a single and potentially life saving treatment.
Hospital	Early diagnosis and prompt early treatment with potent antimalarials Treatment of complications Keep fluid and electrolytes balance Avoid harmful adjuvant treatments Supportive treatment (Follow WHO 2000 guidelines)

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### SEVERE MALARIA

Early and appropriate antimalarial chemotherapy may prevent the development of severe disease.<sup>22</sup> In even small health centers, oral treatment with tablets, capsules or suppositories formulations (in those who are vomiting), may be the best strategy for local health personnel or village health workers. In practice, it is not always possible to distinguish malaria and acute lower respiratory tract infection hence the need to provide these medications. Patients in whom severe malaria is suspected should be transferred to the highest level of medical care available (Table 4), but other factors such as seasonal flooding, lack of vehicles or the condition of the patient can make this impossible.

In treating malaria, early treatment with a potent

antimalarial drug preferably by a parenteral route is important. The earlier treatment is started, the better the prognosis. Drug doses are calculated by body weight and the response monitored clinically and parasitologically. Patients should be monitored for the side-effects of antimalarial drugs. Quinine-induced hypoglycemia may occur during recovery, 3-4 days after the start of treatment, and is particularly common in children and pregnant women. In patients with 'algid malaria', the possibility of a concomitant secondary gram-negative septicemia should be considered and appropriate broad spectrum antibiotics should be given. In the recovery phase, antimalarial drugs should be given by the oral route as soon as possible (Table 5).

Chloroquine is still the drug of choice for chloroquine-sensitive *P. falciparum* malaria in some

areas of Africa. Quinine and quinidine are the only widely available drugs which are effective against chloroquine-resistant strains. Qinghaosu (artemisinin: an ancient Chinese herbal medicine) and its derivatives have been used successfully in treating both uncomplicated and severe falciparum malaria. Their effectiveness in eliminating parasites has been widely established but recrudescence rate can be rather high (10-30%). The recrudescence rate depends upon the dose, duration of artemisinin derivatives used and the severity of disease: the more severe the higher the chance of recrudescence. Intravenous/intramuscular artesunate (2.4 mg/kg iv or im, followed by 1.2 mg/kg injection at 12, 24 hr then daily for 5 days) is effective but not readily generally available in some countries. Intramuscular artemether (3.2 mg/kg im injection followed by 1.6 mg/kg at 12, 24 hr then daily for 5 days) is also effective and the drug is generally available in most countries. Recently, intramuscular arteether (Artemotil<sup>®</sup>), developed by a Dutch company with WHO/TDR support has proven safe and effective for the treatment of severe malaria. It is useful in remote areas where intravenous equipment is not available.

WHO/TDR has also concentrated efforts on the potential of artesunate in suppository form to cure parasites rapidly and significantly to reduce mortality of severe *P. falciparum* malaria. This suppository may prove life-saving.

### POTENTIAL FUTURE DRUGS

The ideal antimalarial drugs should be cheap, well-tolerated oral drugs available in a short course for the treatment of uncomplicated falciparum malaria. For severe malaria, a potent antimalarial drug either iv, im or rectal administrative is needed. Effective adjunctive therapy should also be investigated.

The antimalarial activity of artemisinin derivatives (but not artemisinin itself) is due to the metabolite dihydroartemisinin. Oral dihydroartemisinin treatment produces cure rates and parasite-clearance times

equivalent to oral artesunate. Dihydroartemisinin can be manufactured more cheaply. However, its pharmacokinetic and pharmacodynamic properties vary greatly. Artelinic acid, currently under development, is a water-soluble artemisinin derivative that is more stable in solution than artesunate. Trioxanes, simplified analogues of artemisinin retaining the crucial endoperoxide bridge, are being developed but have not yet entered clinical trials.

Pyronaridine, a Mannich base synthesized by Chinese scientists, is effective in chloroquine-resistant *P. falciparum*. In Thailand, 28-day follow-up after a 5-day pyronaridine course demonstrated a 12 percent recrudescence rate<sup>23</sup>, suggesting that it could be used best in combination with an artemisinin derivative. Formulation and dose optimization studies for using artemisinin with pyronaridine are in progress.

Two new potent 8-aminoquinolones, tafenoquine and CDRI 80/53, are undergoing clinical trials.<sup>24,25</sup> Other potential agents in development are phosphatidyl choline, orotic acid analogues and inhibitors of aspartate and cysteine proteases.

### CONCLUSION

The production of new antimalarials will never keep pace with resistance of existing drugs. Resistance is the prime determinant of a drug's life-span.<sup>26</sup> Setting effective drug regimens must rank as the number one in priority in malaria research and control programs. Rational deployment of new antimalarial drugs and sensible prescribing are effective ways in protecting drug efficacy and reducing the likelihood of resistance. In common with the treatment of other diseases, 'extra mileage' may be obtained from existana compounds by formulating drug combinations and by rotating the use of antimalarials.

### References

1. Rosenthal PJ, Miller LH. The need for new approaches to antimalarial chemotherapy. In: Rosenthal PJ, ed.

- Antimalarial Chemotherapy. New Jersey: Humana Press, 2001:1-13.
2. Olliaro PL, Milhours WK. The antimalarial drug portfolio and research pipeline. Antimalarial chemotherapy. In: Rosenthal PJ, ed. Antimalarial Chemotherapy. New Jersey: Humana Press, 2001:219-32.
  3. Looareesuwan S, Olliaro P, White NJ, et al. Consensus recommendation on the treatment of malaria in Southeast Asia. Southeast Asian J Trop Med Public Health 1998;29:355-60.
  4. Looareesuwan S, Wilairatana P, Chokeyjindachai W, et al. Research on new antimalarial drugs and the use of drugs in combination at the Bangkok Hospital for Tropical Diseases. Southeast Asian J Trop Med Public Health 1998;29:344-54.
  5. Looareesuwan S, Wilairatana P, Chalermrut K, et al. Efficacy and safety of atovaquone/proguanil compared with mefloquine for treatment of acute *Plasmodium falciparum* malaria in Thailand. Am J Trop Med Hyg 1999;60:526-32.
  6. Looareesuwan S, Wilairatana P, Glanarongran R, et al. Atovaquone and proguanil hydrochloride followed by primaquine for treatment of *Plasmodium vivax* malaria in Thailand. Trans R Soc Trop Med Hyg 1999;93:637-40.
  7. Looareesuwan S, Viravan C, Vanijanonta S, et al. Randomised trials of artesunate and mefloquine alone and in sequence for acute uncomplicated falciparum malaria. Lancet 1992;339:821-4.
  8. Bunnag D, Karbwang J, Harinasuta T. Artemether in the treatment of multiple drug resistant falciparum malaria. Southeast Asian J Trop Med Public Health 1992;23:762-8.
  9. Looareesuwan S, Wilairatana P, Viravan C, et al. Open randomized trial of oral artemether alone and sequential combination with mefloquine for acute uncomplicated falciparum malaria. Am J Trop Med Hyg 1997;56:613-7.
  10. Looareesuwan S, Wilairatana P, Vanijanonta S, et al. Monotherapy with artesunate for uncomplicated falciparum malaria: a comparison of 5-day and 7-day regimens. Acta Tropica 1997;67:197-205.
  11. Looareesuwan S, Wilairatana P, Molunto W, et al. A comparative clinical trial of sequential treatments of severe malaria with artesunate suppository followed by mefloquine in Thailand. Am J Trop Med Hyg 1997;57:348-53.
  12. Looareesuwan S, Wilairatana P, Vanijanonta S, et al. Efficacy and tolerability of a sequential, artesunate suppository plus mefloquine, treatment of severe falciparum malaria. Ann Trop Med Parasitol 1995; 89:469-75.
  13. Wilairatana P, Viriyavejakul P, Looareesuwan S, et al. Artesunate suppositories: an effective treatment for severe falciparum malaria in rural areas. Ann Trop Med Parasitol 1997;91:891-6.
  14. Wilairatana P, Krudsood S, Silachamroon U, et al. Clinical trial of sequential treatments of moderately severe and severe malaria with dihydroartemisinin suppository followed by mefloquine in Thailand. Am J Trop Med Hyg 2000;63:290-4.
  15. Looareesuwan S, Wilairatana P, Vanijanonta S, et al. Treatment of acute uncomplicated falciparum malaria with oral dihydroartemisinin. Ann Trop Med Parasitol 1996;90:21-8.
  16. Wilairatana P, Chantavanich P, Singhasivanon P, et al. A clinical trial of dihydroartemisinin for the treatment of acute uncomplicated falciparum malaria in Thailand: a comparison of three different formulations. Int J Parasitol 1998;28:1213-8.
  17. Looareesuwan S, Schilizzi BM, Oosterhuis B, et al. Dose-finding and efficacy study for i.m. artemotil (beta-artether) and comparison with i.m. artemether in acute uncomplicated *P. falciparum* malaria. Br J Clin Pharm 2002;53:492-500.
  18. Looareesuwan S, Vanijanonta S, Viravan C, et al. Randomised trial of mefloquine-tetracycline, and quinine-tetracycline for acute uncomplicated falciparum malaria. Acta Tropica 1994;57:47-53.
  19. Looareesuwan S, Viravan C, Vanijanonta S, et al. Randomised trial of mefloquine-doxycycline, and

- artesunate-doxycycline for treatment of acute uncomplicated falciparum malaria. *Am J Trop Med Hyg* 1994;50:784-9.
20. Looareesuwan S, Wilairatana P, Chocejindachai W, et al. A randomized, double-blind, comparative trial of a new oral combination of artemether and benflumetol (CGP 56697) with mefloquine in the treatment of acute *Plasmodium falciparum* malaria in Thailand. *Am J Trop Med Hyg* 1999;60:238-43.
  21. van Vugt M, Wilairatana P, Gemperli B, et al. Efficacy of six doses of artemether-lumefantrine (benflumetol) in multidrug-resistant *Plasmodium falciparum* malaria. *Am J Trop Med Hyg* 1999;60:936-42.
  22. World Health Organization. Severe falciparum malaria. *Trans R Soc Trop Med Hyg* 2000;94(Suppl 1):1-90.
  23. Looareesuwan S, Kyle DE, Viravan C, et al. Clinical study of pyronaridine for the treatment of acute uncomplicated falciparum malaria in Thailand. *Am J Trop Med Hyg* 1996;54:205-9.
  24. Newton P, White NJ. Malaria: New developments in treatment and prevention. *Ann Rev Med* 1999;50:179-2.
  25. Walsh DS, Looareesuwan S, Wilairatana P, et al. Randomized dose-ranging study of the safety and efficacy of WR 238605 (Tafenoquine) in the prevention of relapse of *Plasmodium vivax* malaria in Thailand. *J Infect Dis* 1999;180:1282-7.
  26. Looareesuwan S, Harinasuta T, Chongsuphajaisiddhi T. Drug resistant malaria with special reference to Thailand. *Southeast Asian J Trop Med Public Health* 1992;23:621-34.