

# Developing artemisinin based drug combinations for the treatment of drug resistant falciparum malaria: A review

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## ABSTRACT

The emergence and spread of drug resistant malaria represents a considerable challenge to controlling malaria. To date, malaria control has relied heavily on a comparatively small number of chemically related drugs, belonging to either the quinoline or the antifolate groups. Only recently have the artemisinin derivatives been used but mostly in south east Asia. Experience has shown that resistance eventually curtails the life-span of antimalarial drugs. Controlling resistance is key to ensuring that the investment put into developing new antimalarial drugs is not wasted.

Current efforts focus on research into new compounds with novel mechanisms of action, and on measures to prevent or delay resistance when drugs are introduced. Drug discovery and development are long, risky and costly ventures. Antimalarial drug development has traditionally been slow but now various private and public institutions are at work to discover and develop new compounds. Today, the antimalarial development pipeline is looking reasonably healthy. Most development relies on the quinoline, antifolate and artemisinin compounds. There is a pressing need to have effective, easy to use, affordable drugs that will last a long time. Drug combinations that have independent modes of action are seen as a way of enhancing efficacy while ensuring mutual protection against resistance. Most research work has focused on the use of artesunate combined with currently used standard drugs, namely, mefloquine, amodiaquine, sulfadoxine/pyrimethamine, and chloroquine. There is clear evidence that combinations improve efficacy without increasing toxicity. However, the absolute cure rates that are achieved by combinations vary widely and depend on the level of resistance of the standard drug. From these studies, further work is underway to produce fixed dose combinations that will be packaged in blister packs.

This review will summarise current antimalarial drug developments and outline recent clinical research that aims to bring artemisinin based combinations to those that need them most.

**KEY WORDS:** Malaria, treatment, drug resistance, drug combination

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## Malaria Burden and Strategies for Control

Malaria is a serious global health challenge. Estimates of the global burden vary but a figure of 400 to 600 million cases per year seems reasonable.<sup>1,2</sup> The vast majority of cases are in African children under five, estimated at 200-500 million cases per year with 0.7 to 2.7 million deaths. Although the burden of malaria and the focus of its control is Africa, malaria is still an important public health problem in other tropical areas such as India, Indonesia, Papua New Guinea, and the Amazon region of Latin America. Of the four species of human malaria, *Plasmodium falciparum* and *Plasmodium vivax* account for the vast majority of cases but *P. falciparum* is the form that causes substantial morbidity and almost all of the mortality.

The strategies currently employed to control malaria include integrated vector control, the use of impregnated bed nets,

reducing parasitaemia and anaemia in pregnant women through intermittent presumptive treatment, and rapid access to reliable diagnosis and effective treatment. Chemotherapy is, therefore, a major element of malaria control and has been adopted by the WHO as a sustainable and realistic approach. The stated aim of Roll Back Malaria is to reduce the malaria mortality in African children by half by the year 2010.<sup>3</sup> This is an ambitious target that could be achieved provided certain criteria are met. These include:

(i) evidence of drug efficacy and safety, (ii) availability of sufficient quantities of drugs to meet the need, (iii) affordability, (iv) political commitment on the part of Governments to change drug policy, and (v) a well thought out strategy to make the change in drug policy.

## Malaria Parasite Resistance to Antimalarial Drugs

Compounding the seriousness of malaria related morbidity and

mortality is drug resistance. *P. falciparum* is now resistant to several commonly used antimalarial drugs. Chloroquine, the mainstay of malaria treatment for the past fifty years, is now ineffective in almost all malaria endemic countries.<sup>4</sup> Chloroquine sensitive *P. falciparum* is confined to Central America, the Dominican Republic and Haiti.<sup>1</sup> Sulfadoxine/pyrimethamine (SP), a widely used inexpensive alternative to chloroquine, has been ineffective in SE Asia and the Amazon basin for several years, and is now losing efficacy in parts of Asia and Africa.<sup>5</sup> Quinine, the mainstay for the treatment of multidrug resistant malaria and severe malaria in many countries, is still effective despite reports of reduced sensitivity.<sup>6</sup> A recent development has been the emergence of chloroquine resistant *P. vivax* which has been reported in focal areas of India, Burma, Papua (Indonesia), Papua New Guinea, Brazil, Guyana, Colombia, and the Solomon Islands (Shapira A, personal communication).<sup>7-13</sup> In Papua, CRPV now constitutes a significant public health problem.<sup>14</sup> Chloroquine resistant *P. malariae* has also been described in Indonesia.<sup>15</sup>

The impact of drug resistant falciparum malaria is considerable.<sup>16</sup> Increased childhood morbidity and mortality in Africa due to chloroquine resistance is now well documented.<sup>17</sup> Malaria related anaemia itself is an important cause of morbidity and mortality, affecting an estimated 1.5 to 6 million African children and is associated with a case fatality rate (CFR) of 15%.<sup>18,19</sup> From a drug policy perspective, drug resistance is the most critical factor in reducing the useful life span of a drug and undermining drug policy.<sup>20</sup>

The main mechanism underlying the development of resistance is naturally occurring genetic mutations in the malaria parasite that confer a survival advantage. These mutations result in a decline in drug sensitivity that depends on the class of antimalarial drug.<sup>21</sup> Inadequate treatment (e.g. sub therapeutic dose, sub optimal drug) of a high biomass infection will not kill mutant parasites and is the main selective pressure for resistance. Resistant parasites are then transmitted to other individuals by mosquitoes. In addition, drugs with long half-lives are more likely to select for resistance because low drug concentrations linger and are only able to kill sensitive parasites.<sup>22</sup>

### **Strategies to Overcome Drug Resistance – The Role of Combination Therapy**

Experience from other infections and cancer chemotherapy have shown that cure rates can be sustained by using combinations of drugs and that this strategy protects drugs in a mutual fashion. The use of single drugs that are easily prone to resistance limits therapeutic choice and can have serious public health consequences. This is particularly true for infections like malaria, leprosy, TB, and HIV/AIDS for which a limited number of drugs are available. The options for malaria treatment are confined to the following drugs: chloroquine, amodiaquine, sulphadoxine/pyrimethamine (SP), mefloquine, artesunate, dihydroartemisinin, the recently registered chlorproguanil/dapsone (LapDap), atovaquone/proguanil, dihydroartemisinin-piperaquine, and artemether/lumefantrine. Appreciable resist-

ance exists today against chloroquine and SP.

The idea that drug combinations could be used to delay anti-malarial drug resistance came from Peters.<sup>23</sup> This was first tried in Thailand using a combination of mefloquine and SP but this failed, primarily because there was already widespread SP resistance. The next attempt was also in Thailand when mefloquine (15mg/kg) began to fail. An increase in the dose of mefloquine (25mg/kg) led to a transient and modest rise in efficacy. Artesunate (4mg/kg/d) for three days was added and this resulted in high cure rates (~95%).<sup>24</sup> Longitudinal data from western Thailand have shown remarkably that these high cure rates have been sustained, transmission has been reduced, and that the *in vitro* sensitivity of malaria parasites to mefloquine has increased.<sup>25</sup>

The underlying science behind the therapeutic effect of the artemisinin based combinations is that the artemisinin kills rapidly and substantially most of the parasites; those that remain are then killed by a high concentration of the companion drug. The efficacy and short half life ( $\leq 1$  hour) of the artemisinins offer protection against resistance.<sup>26</sup> The long half life companion drug is needed to act for long enough in order to kill the rest of the parasites. In this way, the probability that mutant parasites survive and emerge from these two drugs is low. The currently used companion drugs have half lives that vary from several days (e.g. SP) to weeks (e.g. mefloquine). The question regarding the need of matching pharmacokinetic profiles of the combinations is still being debated. Some contend that lingering drug concentrations of unprotected drug (as is the case in all artemisinin-containing regimens) will continue to provide selective pressure for the emergence of resistant parasites.

It is believed that the key to success is to use combination drugs to which parasites are still sensitive. *In vivo* resistance to the artemisinins has not been described but it can be induced in the laboratory.<sup>27</sup> There is ample evidence as to the comparative ease at which resistance develops to standard antimalarial drugs when used alone. We should not wait until these valuable partner drugs have poor efficacy.

### **Taking the Concept of Combination Therapy Forward**

In these days of evidenced based medicine, both international and national public health bodies need to make rational recommendations based on sound data. As a first step, it was agreed in 1998 by WHO/TDR, with USAID funding, and the Wellcome Trust, to commence a series of clinical trials to assess the efficacy and tolerability of artesunate combined with three standard antimalarial drugs (chloroquine, amodiaquine or SP) in Africa (11 trials in 8 countries) and Latin America.<sup>28</sup> WHO/TDR was to be the co-ordinating body.

The aim was to use these drugs in countries where their efficacy was no less than 75% and to choose established and emerging research centres in order to build research capacity. Chloroquine was used only in West Africa; the other two drugs were used across Africa. In Latin America, amodiaquine was used



in Colombia (trial on going) and SP in Peru. Apart from the Peruvian study, these were randomised, double blind, placebo controlled trials that were conducted under Good Clinical Practices (GCP). Common clinical protocols and one analytical plan were developed by WHO/TDR and outside experts so that an individual patient data (IPD) meta-analysis could be done. Collectively, these trials represent the largest series of antimalarial drug trials ever conducted in Africa. The primary efficacy end points were parasitological cure at Days 14 and 28. Secondary efficacy parameters were parasite and fever clearance, and gametocyte carriage rates. Studies included molecular genotyping to distinguish between recrudescence infections and re-infections, PCR for mutations conferring drug resistance, and population pharmacokinetic assessments. Artesunate-placebo was provided by Sanofi/Guilin, amodiaquine by Warner-Lambert/Parke-Davis (now Pfizer), and SP by IDA. All the SP studies had three arms: SP alone, and two dosing regimens of artesunate, administered once daily for one or three days at 4mg/kg/day. The chloroquine and amodiaquine studies used three days of artesunate. Several studies have been published, other studies and the IPD meta-analysis are in press.<sup>29,30</sup> The meta-analysis includes also eligible artesunate plus mefloquine studies conducted in Thailand by the Wellcome Trust and Mahidol University.<sup>31</sup>

The clinical trials that were conducted under the auspices of TDR had the force of numbers behind them. The results were clear: adding artesunate (an artemisinin derivative) had a profound positive effect when added to a standard antimalarial drug without adding to toxicity. This proved a key principle. As a result, further interest in developing artemisinin based combinations was given a boost, deployment studies were organised, and WHO has endorsed fully the use of artemisinin based combinations for treating falciparum malaria.<sup>32</sup>

### **The Global Antimalarial Drug Pipeline**

Historically, antimalarial drugs have come onto the market slowly, but prospects are looking brighter. In the past ten years, several drugs have become available, though only few have received marketing authorisation in western countries and become widely available on the open market. These latter drugs are atovaquone-proguanil (for treatment and prophylaxis of malaria), injectable arteether (also known as artemotil) and artemether (both for the treatment of severe malaria), and artemether-lumefantrine (Co-artemether, for the treatment of uncomplicated falciparum malaria). Other drugs, essentially artemisinin derivatives as single agent (e.g. dihydroartemisinin) or combination therapies (e.g. dihydroartemisinin-piperaquine) have also been developed and registered locally in the country of origin (mainly China) and in several disease-endemic countries. Availability, access, affordability of efficacious medications are all essential elements of malaria control. By contrast, expensive, sub-standard quality, and fake drugs, and inadequate coverage are barriers to enhanced malaria control.

The new efficacious drugs are currently too expensive for widespread use in the public sector of many malaria endemic coun-

tries. Research and development of promising drugs for neglected diseases has tended to fall on the shoulders of the public sector. Drug development now demands high standards of research and data validation in order to meet international standards of registration. The latter is an important consideration for eligibility for the WHO Essential Drug List and for drug procurement.

Happily, a number of drugs and drug combinations are in various stages of development that will meet international regulatory standards. The majority of these drugs will be used for treating uncomplicated falciparum malaria. Funding for these projects is from the private and public sectors. Below, we describe briefly those drugs pertinent to the treatment of acute, uncomplicated falciparum malaria.

*Chlorproguanil-dapsone (LapDap)*. This a non-artemisinin containing, fixed-dose, antifolate combination similar to SP that has been developed jointly by Glaxo Smith Klein, Liverpool university, and WHO/TDR.<sup>33</sup> Both drugs have shorted half lives than the corresponding components of SP. LapDap has been shown to be more efficacious than SP in East Africa.<sup>34</sup>

It shares similar genetic mechanisms of resistance as S/P. This might limit the use of the LapDap combined with artesunate (CDA), which is currently being developed, if there is widespread use of SP and LapDap and consequential development of drug resistance. The CDA development project is a partnership between Medicines for Malaria Venture (MMV), GSK and WHO/TDR.

*Artemether/lumefantrine (Riamet®; Coartem®)*. This is currently the only fixed-dose, artemisinin based combination. The six dose regimen is highly efficacious against multidrug resistant *P. falciparum*.<sup>35</sup> It is also well tolerated. Both components of this combination were originally studied and developed in the Peoples Republic of China by the Academy of Military Medical Sciences (AMMS), Beijing and Kunming Pharmaceutical Factory (KPF), Kunming. The combination was registered in 1992 in China. In a collaboration between the Chinese developers and Novartis, Coartemether was registered in 1999 in Switzerland. It is marketed under a dual-branding, dual-pricing, strategy. Riamet® is available in developed, non-endemic countries and Coartem® is registered and marketed in malaria-endemic countries. Recently, an agreement was reached between Novartis and the WHO for the drug to be available to the public sector of developing countries at a preferential price. Work between Novartis and WHO has led to a more user-friendly packaging of the 6-dose regimen. A paediatric formulation for children under 11kg is currently under development.

*Dihydroartemisinin/Piperaquine (DHA/PPQ)*. DHA/PPQ has been developed and registered in China under the brand name Artekin™. It is also registered in Cambodia. It has been evaluated extensively in clinical trials in Thailand, Vietnam, Cambodia, and China, including Hainan island where PPQ resistance is common following mass prophylaxis. Efficacy has been high and tolerability very good.<sup>36</sup> Piperaquine (PPQ) is an orally active bisquinoline that is approximately equivalent to CQ



against sensitive parasites and significantly more effective than chloroquine against resistant *P. falciparum*. Extensive use of piperazine alone in China found it to be well tolerated. DHA is the main metabolite of the artemisinins and has equivalent clinical efficacy to its parent compounds. A development programme is in the process of being put together with several partners to have DHA/PPQ developed further to be registered in Europe.

*Artesunate-amodiaquine (AS-AQ) & artesunate-mefloquine (AS-S/P)*. AS-MQ, a non-fixed, combination, has been widely used in Thailand and other parts of the South East Asia. It is highly effective against multidrug resistant falciparum malaria and is well tolerated. The efficacy of AS-AQ in the TDR sponsored trials was variable but acceptable in areas where the level of AQ resistance was low. Both these drugs are being developed as fixed dose combinations that will involve all the pertinent preclinical and clinical studies required for European registration. A consortium of partners has been put together with European Commission funding.

*Artesunate/pyronaridine (AS/PRN)* is another artemisinin based combination in the early stages of development. PRN is a Mannich base, antimalarial compound that has been synthesized, developed, and registered in China. It has been used as treatment for malaria since the 1980s. A tablet formulation has proven efficacy against drug resistant falciparum malaria in Africa but was less effective in Thailand.<sup>37,38</sup> However a capsule formulation was 100% effective and well tolerated in Thai patients with uncomplicated malaria at 12 mg/kg for three days (S. Looareesuwan, personal communication). The fixed combination is being developed by MMV with a South Korean company, Shin Poong, and WHO/TDR. Phase II studies with the fixed combination are to start soon.

*Other drugs and developments.* A novel compound, fosmidomycin, has recently been tested in small numbers of patients. Fosmidomycin inhibits 1-deoxy-D-xylulose 5-phosphate reductoisomerase, an enzyme of the nonmevalonate pathway of isoprenoid biosynthesis, which is absent in humans but present in many pathogens and plants. Fosmidomycin was well tolerated but produced modest cure rates.<sup>39,40</sup> However, it is a drug worthy of more trials and could be used in combination with other antimalarials (e.g. clindamycin).

Astesunate plus SP showed modest cure rates in East Africa but was highly efficacious in the Gambia.<sup>29</sup> Again, the underlying resistance of SP proved high in East Africa. Because this combination will still have use in areas where SP resistance is low, a blister pack of AS-S/P has been developed using aged based dosing and is being used in clinical trials in Africa.

### **Where Do We Go from Here ?**

It is of some comfort that there are several artemisinin based combinations in the development pipeline. Never the less, continuing research is needed to develop new antimalarial drugs with different mechanisms of actions that will have long therapeutic life spans. Drug resistance can develop easily and

spread within five years in areas of low malaria transmission.<sup>4</sup> Continual surveillance is required. More research is also needed to ascertain how well new drugs can be deployed in a health system and what public health and economic impacts these drugs have.

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