Artemisinin-Based Combination Treatment of Falciparum Malaria

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Abstract. Artemisinin-based combination treatments (ACTs) are now generally accepted as the best treatments for uncomplicated falciparum malaria. They are rapidly and reliably effective. Efficacy is determined by the drug partnering the artemisinin derivative and, for artesunate–mefloquine, artemether–lumezantrine, and dihydroartemisinin–piperaquine, this usually exceeds 95%. Artesunate–sulfadoxine–pyrimethamine and artesunate–amodiaquine are effective in some areas, but in other areas resistance to the partner precludes their use. There is still uncertainty over the safety of artemisinin derivatives in the first trimester of pregnancy, when they should not be used unless there are no effective alternatives. Otherwise, except for occasional hypersensitivity reactions, the artemisinin derivatives are safe and remarkably well tolerated. The adverse effect profiles of the artemisinin-based combination treatments are determined by the partner drug. Most malaria endemic countries have now adopted artemisinin-based combination treatments as first-line treatment of falciparum malaria, but in most of these only a minority of the patients that need artemisinin-based combination treatments actually receive them.

INTRODUCTION

Falciparum malaria is a mass killer that went out of control. The drug treatments for this potentially lethal infection that have been most widely recommended and provided over the past 50 years (i.e., chloroquine and sulfadoxine–pyrimethamine) no longer work in most tropical countries. Resistance to these drugs emerged in Asia and South America and spread to Africa. As resistance worsened, morbidity and mortality rose as a direct consequence. But this was not appreciated because surveillance was poor, and the clinical and epidemiologic methods used to measure morbidity, mortality, and drug resistance were insensitive. After much procrastination the seriousness of the situation was finally appreciated in the 1990s, although antimalarial policy did not change from ineffective to effective antimalarial drug treatment until the past 3 years in most countries. Replacing the failing chloroquine and sulfadoxine–pyrimethamine with effective drugs required increased donor support because most endemic countries could barely afford the failing medicines, let alone more expensive ones. This was not forthcoming initially. Fortunately things are changing for the better. There is now considerably more funding available for malaria control in endemic countries, particularly from the Global Fund (GFATM). The treatments now recommended by the World Health Organization and supported by the GFATM for uncomplicated falciparum malaria are artemisinin-based combination treatments (ACTs); these are combinations of an artemisinin derivative and, for artesunate–mefloquine, artemether–lumezantrine, and dihydroartemisinin–piperaquine, which results in increased transcription, and therefore true failure rates up to 60%.5 Most identified mechanisms of antimalarial drug resistance result from genetic changes in the human host—although most symptomatic infections are caused by between 107 and 1012 parasites. The theory underlying combination drug treatment of tuberculosis, leprosy, and HIV infection and many cancers is now well known, and the same general principle is now widely accepted for malaria. If two drugs are used with different modes of action, and therefore different resistance mechanisms, then the per-parasite probability of developing resistance to both drugs at the same cell division is the product of their individual per-parasite probabilities.3–6 This is of particular relevance to malaria because on any one day there are only about 1017 malaria parasites in the entire world.7,8 Most identified mechanisms of antimalarial drug resistance result from genetic mutation. Mutation rates for eukaryotes are of the order of 1 in 106 divisions but viable resistant mutant parasites are selected at much lower frequencies. Gene duplications occur more readily than mutations throughout the parasite genome and may also contribute to drug resistance. Amplification of Pfmdr, which results in increased transcription, and therefore more of this protein “pump” per cell, is the main contributor to mefloquine resistance, but at a fitness cost for the parasite.9,10 The highest frequencies documented for the de novo emergence of mutations conferring drug resistance in acute malaria in humans are for atovaquone and pyrimethamine at around 1 in 1012 parasites.7 So if the per parasite probability of developing resistance to 2 drugs (A and B) are both high at 1 in 1012, then a simultaneously resistant mutant (i.e., resistant to both A and B) will arise spontaneously every 1 in 1024 parasites. But because there is a cumulative total of less than 1020 malaria parasites in existence each year, such a simultaneously resistant parasite would arise spontaneously roughly once every 10,000 years, provided the drugs always con-
fronted the parasites in combination. Thus provided the de novo per parasite probability of developing resistance is not much higher than 1 in $10^{12}$ cell divisions and both drugs are present together at inhibitory concentrations, then combinations markedly delay the emergence of resistance. But for ACTs, because the artemisinin derivatives are eliminated rapidly, and the partner drugs are eliminated slowly, there is complete protection only for the artemisinin derivative. The combination still provides good protection against the emergence of resistance to the partner drug, but once resistance has developed the residual concentrations of unprotected partner drug do provide a selective filter enhancing the spread of resistance to the partner compound.

Figure 2 shows the pharmacokinetic–pharmacodynamic rationale for ACTs using artesunate–mefloquine as an example.

Although parasite lines with reduced susceptibility can be selected in the laboratory, therapeutically significant resistance to the artemisinin derivatives has not yet been identified. High-grade stable artemisinin resistance cannot be confirmed yet in the laboratory, which suggests that it may be a rare event. The recent report that some parasites from French Guyana with mutations in the gene encoding the putative target PfATPase6 were highly resistant to artether raised concerns, but these parasites have not been cultured, and this finding must be confirmed. Treatment failure rates are higher and parasite clearance times longer with ACTs in Western Cambodia than elsewhere, the epicentre of drug resistance in Southeast Asia. Even if reduced susceptibility to artemisinin derivatives is not substantiated, and despite the reassuring laboratory studies, it would still be foolish to assume that resistance to these valuable drugs will not happen. If high-level stable resistance to the artemisinin drugs does arise it would be a disaster for the malaria-affected world because they are now the cornerstone of antimalarial treatment. For mutual protection against the emergence of drug resistance, these drugs should be used only in combination with other antimalarials, such that no parasite “sees” the artemisinin component without the other drug being present.

Artemisinin derivatives are particularly effective in combinations because of their high killing rates (parasite reduction ratios RR circa 10,000 fold per cycle), lack of adverse effects, and absence of significant resistance. In ACTs a 3-day treatment course exposes 2 asexual cycles and so reduces the number of parasites in the body by approximately one hundred million-fold. The gametocytocidal activity of the artemisinin compounds is an important bonus reducing transmis-
The individual patient parasite burden (approximating to 2% parasitemia in an adult) is shown on the vertical axis in a logarithmic scale, and the concomitant profile of drug concentrations is shown as a curved red line. The total numbers of parasites exposed to the drugs are shown as triangles, the area of which corresponds to total numbers in the blood. In this example the ACT partner drug is mefloquine. The treatment is given for 3 days, which covers 2 asexual cycles and the effect of the artesunate is a 100,000,000-fold reduction in parasite burden. This leaves approximately 10,000 parasites (dark green triangle B) remaining for residual concentrations of mefloquine (from points m to n) to remove. If no artesunate had been given, the mefloquine would have reduced the parasite burden more slowly (light brown large triangle), and the number of parasites corresponding to B (i.e., B) would have been exposed to lower mefloquine concentrations (from points p to q). In this example these concentrations would be insufficient to inhibit growth of the most resistant parasites prevalent (minimum inhibitory concentration; MIC<sub>P</sub>) and so, whereas the ACT would cure all infections provided these blood concentrations were achieved, there would be treatment failures with mefloquine monotherapy. MIC<sub>P</sub> refers to the most sensitive MICs for artesunate and mefloquine respectively. The time from points x to y on the mefloquine elimination curve represents the window of selection (about 16 days in this example) during which newly acquired infections with sensitive parasites cannot establish themselves whereas resistant parasites can.

Sustainability and thus further reducing malaria incidence in low-transmission settings.12–14

Artemisinin and its derivatives are the most rapidly eliminated of all antimalarials with half-lives of approximately 1 hour. The “ideal” pharmacokinetic properties for an antimalarial drug have been a subject of much discussion. As described, from a resistance prevention perspective, the combination partners should have similar pharmacokinetic properties to provide optimum mutual protection. Slow elimination of the partner drug allows 3-day regimens to be given, but at the price of providing days or weeks of subtherapeutic blood levels that provide a selective filter for resistant parasites acquired from elsewhere, and thereby encouraging the spread of resistance.15–17 (Figure 2). On the other hand these residual “prophylactic” levels suppress new infections giving a period of post treatment prophylaxis (PTP) which, in high-transmission settings, may improve clinical and hematological recovery. Rapid elimination ensures that the residual concentrations do not provide a selective filter for resistant parasites, but rapidly eliminated drugs (if used alone) do not provide any PTP, must be given for 7 days, and adherence to 7-day regimens is poor.18 Incomplete treatment encourages resistance. Even 7-day regimens of artemisinin derivatives (as monotherapy) are associated with approximately 10% failure rates.19,20 Thus to be highly effective in a 3-day regimen, the terminal elimination half-life of at least one drug component must exceed 24 hours (longer for less active drugs) such that concentrations in the fourth drug-exposed asexual cycle (7 to 8 days after starting treatment) are still sufficient to suppress multiplication of the most resistant parasites prevalent.6,7

Provided there is not high-level resistance to the partner drug, then ACTs provide complete protection for the artemisinin derivatives from selection of a de novo resistant mutant if adherence is good (i.e., no parasite is exposed to artemisinin during one asexual cycle without the partner being present), but this does leave the partner’s slowly eliminated “tail” unprotected by the artemisinin derivative. However, because artemisinin and its derivatives reduce parasite numbers by approximately 10,000-fold per 2-day asexual cycle, the residual number of parasites exposed to the slowly eliminated partner drug alone, after 2 asexual cycles of artemisinin exposure, is a tiny fraction (<0.0001%) of those present at the peak of the acute symptomatic infection (Figure 2). Furthermore these residual parasites are exposed to relatively high levels of partner drug and, even if susceptibility was reduced, these levels are usually sufficient to eradicate the infection. But the long elimination phase “tail” of the partner drug does provide a selective filter for resistant parasites acquired from elsewhere, and thereby contributes to the spread of resistance once it has developed. Although the greatest use of antimalarials is in high-transmission areas, historically resistance has emerged and spread most rapidly in low-transmission settings. This illustrates the important role of host immunity in delaying the emergence and spread of resistance.

DEPLOYMENT

The main obstacles to the success of combination treatment in preventing the emergence of resistance will be inadequate treatment (e.g., substandard drugs, incorrect dosing, unusual pharmacokinetics, poor adherence) and, as for antituberculous drugs, use of one of the combination partners alone. This is why blister packing has been encouraged and fixed dose combinations are now being developed and recommended. Cost is a major obstacle to ensuring adequate treatment because patients may not have enough money to purchase a full course of treatment or, once they feel better, will keep the remaining prescribed drugs for themselves or a family member when they next fall ill. Poor quality drugs are common in tropical areas of the world and counterfeit medicines are a major concern. Antimalarials are available widely in the market place, and often sold at incorrect doses or without correct advice. Even when a correct course is obtained adherence to antimalarial treatment regimens is often incomplete. Resistance to the artemisinins may not have happened yet, but it would be unwise to be complacent. If artemisinin resistance does emerge it will most likely arise in a hyperparasitemic patient who received an inadequate dose of a single antimalarial drug (i.e., not in combination with another suitable antimalarial agent).7 Irrespective of the epidemiologic setting, ensuring that patients with high parasitemias receive a full course of treatment with adequate doses of ACTs would be an effective method of slowing the de novo emergence of antimalarial drug resistance.

Ideally, to ensure the maximum useful therapeutic life,
there should be no resistance to the partner drug in an ACT, yet on the Northwestern border of Thailand, an area of low transmission where mefloquine resistance had developed already, systematic deployment of artesunate–mefloquine combination therapy was dramatically effective both in stopping resistance, and also in reducing the incidence of malaria. In fact mefloquine resistance declined after widespread deployment of artesunate–mefloquine. In this setting before ACTs were introduced when mefloquine monotherapy was used, resistant parasites had a survival and transmission advantage—which was negated by the artesunate–mefloquine combination treatment. Mefloquine resistance develops rapidly because gene amplification is a relatively frequent mitotic event in *P. falciparum*, but it may also go rapidly as deamplification is also frequent, and *P*/*f*mdt amplification carries a fitness cost. But for the other drugs and resistance mechanisms involving mutations, deploying an ACT containing a failing drug may not lead to a reversal of resistance, and could eventually leave the artemisinin component inadequately protected as resistance to the partner worsens. Four ACTs are currently recommended by WHO: artesunate–mefloquine, artesunate–sulfadoxine–pyrimethamine (SP), artesunate–amodiaquine, and artemether–lumefantrine. The combinations containing SP and amodiaquine are both threatened by resistance.1

**ACCESS**

Artemisinin-based combination treatments are highly effective and really could make a major contribution to global malaria control, but despite the recent changes in policy in most malaria endemic countries (Figure 1) only a minority of people who need these drugs actually receive them. Cost and access remain formidable obstacles. Few public health structures reach out far enough or efficiently enough to provide good coverage of effective and affordable drugs to rural communities. The Institute of Medicine reviewed and assessed the various deployment options available.23 The review recognized that the private sector still played a major role in antimalarial drug delivery in most tropical countries, and concluded that existing frameworks for antimalarial drug delivery would not provide sufficient ACT coverage to make a major impact on malaria, would not provide sufficient protection against the emergence of artemisinin resistance, and would continue to provide incentives to fake or substandard drugs. The IOM committee recognized the potential contribution ACTs could make to global malaria control and recommended subsidizing the cost of ACTs both to the public and to the private sectors such that these new effective treatments would cost no more than chloroquine to the end user. Thus market forces would drive the ICT distribution. They noted that antimalarial drug resistance has usually arisen in Asia and therefore preventing resistance arising in Asia should benefit Africa. There is increasing support for this initiative, but there is much work to do. The current challenge is to raise sufficient funds, to work out how best to operate such a subsidy, and how to put in place all the necessary monitoring and evaluation mechanisms necessary.

**PHARMACOLOGY**

Artemisinin, the parent drug, has now largely given way to the more potent dihydroartemisinin and its derivatives, artemether, artepotil, and artesunate. The 3 derivatives are all converted back *in vivo* to dihydroartemisinin. Oral absorption is good (bioavailability > 60%) with peak concentrations usually achieved within 4 hours. Dihydroartemisinin has more variable oral bioavailability dependent on the excipients in the oral formulation. All are eliminated rapidly by metabolic biotransformation with half-lives of 1 hour or less (Table 1). Artesunate is readily hydrolyzed at neutral and acidic pH, and deesterification is accelerated by red cell and plasma esterases. Artemether and artepotil are biotransformed more slowly, being demethylated by metabolic transformation (principally by CYP 3A4). These drugs are highly active against all Plasmodium species. The artemisinin derivatives are the most rapidly acting of all antimalarial drugs and pro-

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**Table 1**

Summary of pharmacokinetic properties of antimalarial drugs that have been used in artemisinin combination treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Absorption to peak (h)</th>
<th>Oral dose (mg/kg)</th>
<th>Plasma peak level (mg/L)</th>
<th>Binding (%)</th>
<th>Vd/f (l/kg)</th>
<th>Clearance/f (ml kg⁻¹ min⁻¹)</th>
<th>T½/f (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>5</td>
<td>10</td>
<td>0.12</td>
<td>55</td>
<td>10–1000</td>
<td>2.0</td>
<td>720–1440</td>
</tr>
<tr>
<td>Piperaquine</td>
<td>4–7</td>
<td>32</td>
<td>0.75</td>
<td>&gt; 99</td>
<td>574</td>
<td>15</td>
<td>&gt; 550</td>
</tr>
<tr>
<td>Amodiaquine</td>
<td>4</td>
<td>10</td>
<td>0.37</td>
<td>—</td>
<td>—</td>
<td>4–6</td>
<td>240‡</td>
</tr>
<tr>
<td>Dihydroartemisinin</td>
<td>4</td>
<td>4</td>
<td>0.36</td>
<td>93</td>
<td>—</td>
<td>0.75‡</td>
<td></td>
</tr>
<tr>
<td>Artesunate</td>
<td>1.5</td>
<td>4</td>
<td>0.5</td>
<td>—</td>
<td>0.15</td>
<td>50</td>
<td>0.75‡</td>
</tr>
<tr>
<td>Artemether</td>
<td>2</td>
<td>4</td>
<td>1.5</td>
<td>95</td>
<td>2.7</td>
<td>54</td>
<td>1</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>17</td>
<td>25</td>
<td>1.2</td>
<td>&gt; 98</td>
<td>20</td>
<td>0.35</td>
<td>336</td>
</tr>
<tr>
<td>Halofantrine</td>
<td>15</td>
<td>8</td>
<td>0.9‡</td>
<td>&gt; 98§</td>
<td>—</td>
<td>7.5</td>
<td>113</td>
</tr>
<tr>
<td>Lumefantrine</td>
<td>6</td>
<td>9</td>
<td>3.5‡</td>
<td>&gt; 98§</td>
<td>—</td>
<td>7.5</td>
<td>113</td>
</tr>
<tr>
<td>Pyrimethamine</td>
<td>9</td>
<td>1.25</td>
<td>0.28</td>
<td>94</td>
<td>6.3</td>
<td>1.2</td>
<td>65</td>
</tr>
<tr>
<td>Chlorproguanil</td>
<td>4</td>
<td>2</td>
<td>0.1</td>
<td>—</td>
<td>37</td>
<td>17</td>
<td>35</td>
</tr>
<tr>
<td>Atovaquone¶</td>
<td>6</td>
<td>15</td>
<td>5‡</td>
<td>99.5</td>
<td>6</td>
<td>2.5</td>
<td>30</td>
</tr>
<tr>
<td>Sulfadoxine</td>
<td>24</td>
<td>25</td>
<td>64</td>
<td>88</td>
<td>4–1</td>
<td>0.04</td>
<td>100</td>
</tr>
<tr>
<td>Dapsone</td>
<td>4</td>
<td>2.5</td>
<td>0.9</td>
<td>73</td>
<td>1.5</td>
<td>0.7</td>
<td>27</td>
</tr>
</tbody>
</table>

Vd/f is the total apparent volume of distribution divided by “f”, the fraction of drug absorbed.

T½/f is the terminal phase elimination half-life.

¶ Given in combination with dihydroartemisinin and taken with food.

†Binds to lipoproteins.

‡Absorption increased significantly by fats.

§Binds to lipoproteins.

Δ Pregnancy is usually associated with lower drug concentrations.
duce the fastest clinical responses to treatment. They are noticeably better than other antimalarial drugs. They have a broad spectrum of antimalarial activity acting against the young ring form parasites and preventing their development to the more mature pathogenic stages. This explains the rapid therapeutic responses obtained with the artesunate derivatives. This effect is particularly important in the management of severe malaria, where artesunate has been shown to reduce mortality. Artemether and artemotil have slightly less antimalarial activity than artesunate in vitro but all 3 compounds are readily converted in vivo to dihydroartemisinin, which contributes the majority of antimalarial effect in treatment. Dose regimens of the drugs are similar. In combination with more slowly eliminated antimalarials, the addition of artesunate, artemether, or dihydroartemisinin consistently improves cure rates (unless they were 100% already) and has the advantage of producing a more rapid clinical response to treatment, reduction in gametocyte carriage, and thus malaria transmission, and, when deployed extensively in low-transmission areas, a reduction in malaria incidence. A 3-day course of the artesinin derivative in combination with a slowly eliminated partner drug (elimination half life > 1 day) is required for optimum cure rates. Two-day and 1-day courses are insufficient because they expose only one asexual cycle to the artesinin derivative. If the partner drug is effective then such regimens will still give high cure rates, but they will not provide sufficient protection against the emergence of resistance. There has been some investigation of the optimum dose with in-vivo dose response studies suggesting that at least 2 mg/kg/d for 3 days of artesunate is required for maximal effect. Current ACTs regimens contain between 2.5 and 4 mg/kg of artesinin derivative given daily for 3 days. They are easy to use, and are well tolerated. There are no specific pediatric formulations, although a pediatric formulation of arteether–lumefantrin and fixed dose combinations of artesunate–mefloquine and artesunate–amodiaquine with pediatric tablet sizes have been developed.

### ADVERSE EFFECTS

Artesinin and its derivatives are safe and remarkably well tolerated. There have been reports of mild gastrointestinal disturbances, dizziness, tinnitus, and bradycardia, although none of these associations are convincing. The only potentially serious adverse effect that has been reported with this class of drugs in clinical trials is type 1 hypersensitivity reactions in approximately 1 in 3,000 patients. Transient reticulocytopenia, neutropenia, and elevated liver enzyme values have been reported but none have been clinically significant. Electrocardiographic abnormalities, including prolongation of the QT interval, have also been reported although most studies have not found any significant electrocardiographic abnormalities. Indeed the weight of evidence suggests these drugs have no adverse cardiovascular effects at all. In severe malaria, as with quinine, blackwater fever has been reported. In all species of animals tested, intramuscular arteether and artemolit cause an unusual selective pattern of neuronal damage to certain brain stem nuclei. Neurotoxicity in experimental animals is related to the sustained blood concentrations that follow intramuscular administration of the oil-based derivatives arteether and artemolit, because it is much less evident when the same doses are given orally, or with similar doses of water-soluble drugs such as artesunate, despite transiently higher blood concentrations. With the single exception of one much disputed report, extensive clinical, neurophysiological, and pathologic studies in humans have shown similar findings with therapeutic use of these compounds. Artemisinin and its derivatives inhibit erythropoesis in the early fetus, and cause fetal resorption in all experimental animals tested to date. This can in some circumstances lead to developmental abnormalities in rodents and rabbits. Because these drugs have not been evaluated extensively in early pregnancy in humans, they should be avoided in patients in the first trimester of pregnancy with uncomplicated malaria until more information is available (see below). There is no evidence for adverse effects on the fetus exposed in the second and third trimesters, when these drugs are recommended depending on the safety profile of the partner drug. The safety profile of ACTs is therefore determined by the partner drug. Large-scale safety monitoring or pharmacovigilance is often talked about in the context of antimalarial drugs, but it is difficult, and it is not often done. As deployment increases the ACTs will be used with increasing frequency in individuals. More information on safety with frequent dosing is needed.

### THE ACTS

Chloroquine resistance is now so widespread that it is not included in currently recommended ACTs. Artesunate–SP and artesunate–amodiaquine are used in areas with drug susceptibility to these drugs. In areas where resistance to sulfonamide–pyrimethamine, chloroquine, and amodiaquine is prevalent, then artemisinin combinations with either lumefantrin or mefloquine are the current alternatives. Soon these drugs will be joined by ACTs in fixed dose coformulations containing piperquine, pyronaridine, or chlorproguanil–dapsone. In general, blister-packed oral formulations of these drugs have shelf-lives in tropical conditions of 2 years. Longer shelf-lives would considerably facilitate deployment.

### ARTESESUNATE–SULFADOXINE–PYRIMETHAMINE

Sulfadoxine-pyrimethamine is a fixed combination of a long-acting sulfonamide and the antifolate pyrimethamine. These are synergistic against sensitive parasites. Minor adverse effects are unusual. Serious sulfonamide toxicity is unusual with a single-dose treatment of malaria. The anti-folate properties of pyrimethamine rarely produce toxicity. The combination with artesunate is available as separate scored tablets containing 50 mg of artesunate and tablets containing 500 mg of sulfadoxine and 25 mg of pyrimethamine. There are no plans for developing a fixed dose combination. The total recommended treatment is 4 mg/kg BW of artesunate, given once a day for 3 days and a single administration of sulfadoxine–pyrimethamine 1.25/25 mg base/ kg BW on admission. This SP dose was developed in adults but in the main target group (children aged 2–5 years) the weight adjusted dose produced blood concentrations of both components that are ap-
proximately half those in adults.\textsuperscript{53} Thus the standard dose may be sub-optimal in younger children. The combination has been evaluated extensively in adults and children with uncomplicated malaria and is sufficiently efficacious in areas where 28-day cure rates with sulfadoxine–pyrimethamine alone exceed 80\%.\textsuperscript{52,54} This ACT is currently being used in parts of South America, the Middle East, and South Asia where SP susceptibility remains high. Because sulfadoxine–pyrimethamine, sulfaflene–pyrimethamine, and trimethoprim–sulfamethoxazole (co-trimoxazole) are still widely used as “monotherapies,” resistance is likely to worsen.

\textbf{ARTESTUNE–AMODIAQUINE}

Amodiaquine, like chloroquine, is a 4-aminooquinoline: it is effective against chloroquine-resistant strains of \textit{P. falciparum}, although there is some cross-resistance. In recent years resistance has worsened considerably in parts of East and Southern Africa. After oral administration amodiaquine is largely converted to desethylamodiaquine, which contributes the majority of antimalarial activity. Amodiaquine is generally reasonably well tolerated and slightly more palatable than chloroquine, although in some areas it has not been a popular substitute. The serious adverse effects that have been associated with its prophylactic use (agranulocytosis and severe liver toxicity) are considered rare when amodiaquine is used in malaria treatment, although more data are needed to characterize the risks. More data are also required in pregnancy. The combination of amodiaquine with artesunate is currently available in blister packs as separate scored tablets containing 50 mg of artesunate and 153 mg base of amodiaquine, but co-formulated tablets have been developed recently by the Drugs for Neglected Diseases initiative (DNDi). The total recommended treatment is 4 mg/kg BW of artesunate and 10 mg base/kg BW of amodiaquine once a day for 3 days. Amodiaquine–artesunate has proved to be an efficacious combination in areas where 28-day cure rates with amodiaquine monotherapy exceed 80\%.\textsuperscript{55–57}

\textbf{ARTESTEMU–LUMEFANTRINE}

This was the first fixed dose combination of an artemisinin derivative with a second unrelated antimalarial compound. Lumezantrine (formerly benflumetol) is an aryl aminoalcohol in the same general group as mefloquine and halofantrine. It was discovered and developed in the People’s Republic of China. Lumezantrine is active against all the human malaria parasites, including multi-drug–resistant \textit{P. falciparum} (although there is some cross-resistance with halofantrine and mefloquine). Artemether–lumefantrine is dispensed as tablets containing 80/480 mg respectively. It was introduced originally as a 4-dose regimen given at 0, 8, 24, and 48 hours. This shorter course proved insufficiently efficacious. Pharmacokinetic–pharmacodynamic (PK–PD) studies indicated that the principal PK determinant of cure was the area under the plasma lumefantrine concentration time curve (AUC), or its surrogate, the day 7 lumefantrine level.\textsuperscript{58} Lumezantrine absorption (like that of atovaquone and halofantrine) is critically dependent on co-administration with fats and thus plasma concentrations vary markedly between patients.\textsuperscript{58} In Thailand day 7 levels over 500 ng/mL were associated with > 90\% cure rates. With the 4-dose regimen plasma concentrations of lumefantrine during the third and fourth post-treatment cycles (4–8 days) were insufficient to eradicate all infections. To increase the AUC and thus cure rate, a 6-dose regimen (adult dose 80/480 mg at 0, 8, 24, 36, 48, and 60 hours) was then evaluated.\textsuperscript{59} This has proved highly effective and remarkably well tolerated. Against multi-drug–resistant falciparum malaria the 6-dose regimen of arte–lumefantrine is generally as effective as and better tolerated than artesunate–mefloquine.\textsuperscript{60–64} Artemether–lumefantrine is becoming increasingly available in tropical countries. The excellent adverse effects profile and recent price reductions (down to US $1 per adult treatment) make it an increasingly attractive treatment option. New formulations have also been produced but these must demonstrate comparable bioavailability with the original formulation before they can be recommended. However, the complexity of the treatment (2 doses per day) and the required fat co-administration (albeit small amounts; at least 1.2 g/dose) are obstacles.\textsuperscript{65} Once a day dosing is not an option because absorption is dose limited.\textsuperscript{66} There is increasing evidence of safety for this combination in the second and third trimesters of pregnancy. But plasma concentrations of artemether, the metabolite dihydroartemisinin, and lumefantrine are all significantly reduced in late pregnancy, suggesting that a longer course of treatment may be needed in this vulnerable patient group.\textsuperscript{67}

\textbf{ARTESUNE–MEFLOQUINE}

Mefloquine is a quinoline methanol compound related to quinine.\textsuperscript{68} Several different mefloquine formulations are now available with different oral bioavailability. Employment of mefloquine as monotherapy for the management of malaria has lead to rapid spread of resistance, mediated mainly by an increase in copy number and expression of the \textit{P. falciparum} multi-drug resistance (MDR) gene (\textit{Pfmdr1}).\textsuperscript{69} There is theoretical evidence to suggest that initial deployment of the lower dose of mefloquine encourages resistance, and that initial use of higher doses, preferably in combination with an artemisinin derivative is less likely to lead to resistance.\textsuperscript{70} Where adherence can be assured the dose should be split at 15 mg/kg initially followed 8–24 hours later by a second 10 mg/kg or as 8.3 mg/kg daily for 3 days (this is approximately the dose in the new fixed dose combination). This improves bioavailability and reduces vomiting.\textsuperscript{71} There is no formulation of mefloquine for children. Despite earlier restrictions there is no reason to withhold mefloquine from young children. Limited information suggested that mefloquine was probably safe in pregnancy, although the observation in Thailand of an increased stillbirth risk when mefloquine was used in treatment at any stage of pregnancy has cast uncertainty over its use in pregnant women.\textsuperscript{72} This effect was not seen in large studies conducted in Malawi.\textsuperscript{73} Mefloquine commonly induces nausea, dysphoria, and dizziness, and in approximately 1:1,000 Asian patients, and up to 1:200 Caucasians or African subjects, mefloquine treatment induces a self-limiting acute neuropsychiatric syndrome manifest by encephalopathy, convulsions, or psychosis.\textsuperscript{74} Suicide has been reported. The risks of this acute neuropsychiatric syndrome are increased if the patient has a previous history of psychiatric illness or epilepsy. There is a considerable increase in the risk
if mefloquine is used after severe malaria. Approximately 1:20 patients given mefloquine after recovery from cerebral malaria will have an acute reaction and therefore mefloquine should not be used in this group. Neuropsychiatric reactions are also more common if mefloquine has been used in the previous 2 months, and therefore mefloquine should not be used to treat recrudescent infections occurring within 2 months of treatment. However in practice the principle adverse effect of mefloquine is vomiting. This is more likely in young children, and even if the drug is administered again, low blood levels and an increased risk of treatment failure result. Combining artesunate or artemether (4 mg/kg/day for 3 days) with mefloquine has all the advantages of a combination treatment previously described, and the additional benefit that if mefloquine is split as 8.3 mg/kg/day for 3 days or not given until the second day of treatment then absorption is increased and gastrointestinal adverse effects are lessened. A fixed combination of mefloquine and artesunate has recently been developed. This is dispensed as tablets containing 200 mg of artesunate and 400 mg mefloquine (base). Recent trials in Asia indicated that the tolerability of this new regimen (mefloquine dose 8 mg/kg/d for 3 days) is better than that of the standard regimen. This combination has been evaluated and used mainly in Southeast Asia and South America. More information on tolerability, safety, and efficacy is needed in African children so that its potential utility in Africa can be assessed objectively.

**ARTESUNATE–CHLORPROGUANIL–DAPSONE**

Chlorproguanil–dapsone is an antifol-sulfonamide combination with a similar mode of action and synergistic properties to sulfadoxine–pyrimethamine. Chlorproguanil can be considered as a prodrug for the active antifol chlorcycloguanil to which it is metabolized by the polymorphic CYP450 2C19. Activity of this enzyme is reduced in approximately 20% of Orientals and is also reduced by estrogens (e.g., pregnancy, oral contraceptive). The advantages of this combination are good tolerability and rapid elimination providing less selective pressure on the spread of resistance and greater activity than SP against moderately resistant *Plasmodium falciparum* (although both compounds are ineffective against *P. falciparum* with the Ile164Leu mutation common in Asia and South America, and recently identified in Africa). Disadvantages are resistance selected already by SP, some concerns over the safety of dapsone (hemolytic anemia), and lack of a post-treatment prophylactic effect. Whether this rapidly eliminated drug will be sufficiently effective for patients with high parasite burdens in a 3-day regimen remains to be seen. The ACT is in the late stage development and should be registered in the near future.

**ARTESUNATE–ATOVAQUONE–PROGUANIL**

This fixed dose combination of 2 established drugs has not been developed as a 3-drug fixed dose ACT although it has been evaluated and found to be well tolerated, safe, and effective. Atovaquone–proguanil has a different (and synergistic) mode of action to other antimalarials affecting parasite respiration at the level of the cytochrome chain. Proguanil is acting itself in the combination, and not via the antifol triazine metabolite cycloguanil—so it remains effective against antifol-resistant parasites. Mutations in the gene encoding cytochrome b confer high level atovaquone resistance. Atovaquone absorption (like that of lumefantrine and halofantrine) is augmented by co-administration with fats. Its elimination half-life of 1–2 days provides for an effective 3-day treatment regimen. As with many antimalarials, plasma concentrations of both drugs are reduced in pregnancy. It is remarkably well tolerated with no serious adverse effects. The main impediment to its use is the high cost of atovaquone manufacture. The drug is essentially unaffordable in malaria endemic areas.

**ARTESUNATE–PYRONARIDINE**

Pyronaridine is one of many synthetic antimalarials developed in China and used originally as a monotherapy. It bears closest structural similarity to amodiaquine, although pyronaridine is much more active against resistant parasites. Pyronaridine’s pharmacokinetic properties have not been fully characterized yet but like several other drugs in this general class of antimalarials, it is extensively distributed and eliminated slowly. The mechanism of action of the drug and mechanisms of potential resistance have not been well characterized but are likely to be related to those of the other drugs in this general class. Pyronaridine and the ACT combination are well tolerated and effective. The fixed dose ACT is in late-stage development.

**DIHYDROARTESININ–PIPERAQUINE**

Piperaquine is a bisquinoline compound related to chloroquine and other 4-aminoquinolines. It was discovered in France and developed as an antimalarial by Chinese scientists over 30 years ago. Piperaquine replaced chloroquine as the first-line treatment of falciparum malaria in China in 1978. After over 200 metric tons were used, including in mass treatment, resistance to piperaquine developed in *P. falciparum* in the late 1980s. Piperaquine was not used outside of China. The mechanism of action of the drug and mechanism of resistance have not been well characterized but are likely to be related to those of the other drugs in this general class. Piperaquine has a large apparent volume of distribution of >500 L/kg and a terminal elimination half-life estimated at 2 to 3 weeks. Oral bioavailability increases with co-administration with fat. The fixed dose combination formulated in tablets containing dihydroartemisinin (40 mg) and piperaquine (320 mg) is commercially available in many countries in Asia, and also more recently in Africa. Recent clinical trials have shown that the fixed combination given once daily for 3 days was effective and well tolerated. The most common adverse effects are gastrointestinal (nausea, vomiting, abdominal pain, and diarrhea), but they are usually mild and self-limiting. The main determinant of the parasitological efficacy is the slow elimination of piperaquine. This also determines the “post-treatment prophylactic effect,” which is important if the drug is going to be used as Intermittent Preventive Treatment (IPT). The simplicity of administration, the excellent efficacy even against multi-drug-resistant strains
and the favorable toxicity profile, make the DHA-piperaquine combination one of the more promising of the currently available ACTs.

ACTS IN CHILDREN

The ACTs seem to be tolerated as well or better in children than in adults. There is no specific age-related toxicity. In younger children vomiting or regurgitation of the administered dose are always a concern but are no more common with ACTs than monotherapies. Recent pharmacokinetic studies indicate that the dose regimen advocated for SP in children for many years is probably too low.53 There are insufficient pharmacokinetic data on amodiaquine54 and more data on the pharmacokinetics of piperaquine in children are needed. Dose regimens for artemether–mefloquine and arte- mether–lumefantrine in children are justified by pharmacokinetic studies. Further work is needed to optimize dosing in children based on weight or surface area and, where necessary, to introduce specific pediatric formulations.

ACTS IN PREGNANCY

Pregnant women are a high-risk group. They are more susceptible to malaria, more likely to develop anemia, and if non-immune are more likely to develop complications. Birthweight is consistently reduced by malaria. Therefore, pregnant women desperately need effective and safe antimalarial treatments. The main concern surrounding the general deployment of ACTs is their safety in the first trimester of pregnancy.49–53 Work by Chinese scientists in rodents and rabbits conducted in the 1970s indicated that early pregnancy exposure could induce fetal resorption. Recent reproductive toxicity studies have confirmed that this is a class effect of the compounds and is seen in all experimental animal species studied. It results from a specific inhibition of fetal erythropoiesis. Fetal resorption would result in early pregnancy loss. Much more worrying is the potential to cause developmental abnormality. In rodents and rabbits at doses close to human therapeutic doses, artemisinins given in a critical window in the early stage of gestation, may also cause limb deformation. In primates, doses of 12–30 mg/kg daily given continuously between day 20 and day 50 Pc (equivalent to 20–56 days in human pregnancy) cause fetal resorption and slight (4–7%) long bone shortening, but no abnormalities. No effects were observed at 4 mg/kg.95

Given these uncertainties the artemisinin containing drugs are not indicated for the management of uncomplicated malaria in the first trimester of pregnancy unless there are no effective alternatives. But it is important to emphasise that artemunate should be used in severe malaria where it is clearly superior in terms of life-saving efficacy to quinine. In the second and third trimesters there is increasing evidence of safety for these drugs, with no evidence of adverse effects in over 1,000 prospectively followed pregnancies.96,97 Questions on dosage remain as concentrations of artemunate, arte- mether, and dihydroartemisinin, and several of the partner drugs are reduced in late pregnancy compared with non-pregnant adults.67,98,99 In the second and third trimesters, recommendations are determined more by the evidence for the partner drug. However, there is a grave paucity of data on the safety, the efficacy, and the pharmacokinetic properties of the other antimalarials in pregnancy. For example there are no published pharmacokinetic data on amodiaquine, or sulfadoxine–pyrimethamine despite their extensive deployment. A recent review on the use of antimalarials in pregnancy also emphasizes the lack of data on the safety of some drugs that have been used for decades.97 On the other hand, drugs that are considered safe and for which pharmacokinetic data are available to support current dosing recommendations are either ineffective (e.g., chloroquine) or there are safety concerns (e.g., mefloquine, quinine). Mefloquine was associated with an increased risk of stillbirths in Thailand but not in Malawi.22,73 Quinine is associated with a high risk of hypoglycemia in late pregnancy. Clearly more information on the other drugs is needed urgently. The 2006 edition of the WHO Malaria Treatment Guidelines1 recommends that ACTs should be used in the second and third trimesters of pregnancy. These recommendations were the result of careful examination of the evidence available at the time and will be reviewed and modified by new evidence. It is generally accepted that a drug should first be shown to be safe and effective in treatment before it can be introduced in an IPT strategy.

PLASMODIUM VIVAX

The artemisinin derivatives and the ACTs work as well or better against Plasmodium vivax compared with Plasmodium falciparum infections.100 The exception to this is artesunate–SP, which is ineffective in those areas with high-level antifol resistance in P. vivax. These drugs do not affect the hypnozoites, so relapses are not prevented. The slowly eliminated drugs (e.g., chloroquine, mefloquine, piperaquine) suppress the emergence of the first relapse in the frequently relapsing “tropical strains” of P. vivax so the first successful emergence of a relapse (i.e., the second relapse) typically occurs about 6 weeks after treatment.

EFFECTS ON TRANSMISSION

All effective antimalarials prevent the development of gametocytes in P. vivax, P. malariae, and P. ovale infections and the early-stage gametocytes (stages 1 to 3) of P. falciparum. The artemisinin derivatives inhibit development of more mature P. falciparum gametocytes.12,101 Gametocytemia is greater in recrudescence than primary infections. In low-transmission settings this gametocytocidal effect and the high cure rates obtained with ACTs both contribute to reducing transmission, and thus the incidence of malaria.

CONCLUSIONS

The ACTs are now accepted as the best treatments for uncomplicated falciparum malaria, and policy change has taken place in most countries to make these the first-line recommended drugs. The evidence base for efficacy and safety has grown considerably in recent years as these have become the most studied of all antimalarial drugs. Together with improved diagnosis and appropriate vector control measures, the ACTs should have a significant effect in reducing the burden of malaria throughout the tropical world, but to
achieve this they will need to become more affordable and more available. This would be best achieved by subsidizing their cost both in the public and the private sectors. As deployment of ACTs increases, we will need to invest more in education, health service delivery, monitoring of rare adverse effects, and assessment of resistance to optimize their use, and thereby ensure they have the greatest impact on malaria.

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