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Drug-Resistant Malaria: The Era of ACT

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Abstract

As drug-resistant falciparum malaria has continued to evolve and spread worldwide, artemisinin-based combination therapies (ACT) have become the centerpiece of global malaria control over the past decade. This review discusses how advances in antimalarial drug resistance monitoring and rational use of the array of ACTs now available can maximize the impact of this highly efficacious therapy, even as resistance to artemisinins is emerging in Southeast Asia.

Keywords

Drug-resistant malaria; Artemisinin-based combination therapy; ACT; *Plasmodium falciparum*; Antimalarial resistance

Introduction

Over the past 50 years, the emergence of resistance to commonly used antimalarials has significantly hindered malaria control efforts at great cost to human health and life [1]. Resistance has cut short the therapeutic lifespan of available antimalarials and placed significant stress on control programs. Yet we are now in an age when the World Health Organization (WHO) and others are once again championing the cause of malaria elimination. This effort is in large part made possible by the recognition of a powerful class of antimalarials—the artemisinins. Artemisinins not only achieve rapid clearance of the asexual parasites that cause symptomatic blood-stage infection, but also reduce the numbers of sexual-stage parasites (gametocytes) responsible for transmission. Paired with a second, longer acting partner drug, the resulting artemisinin-based combination therapy (ACT) is expected to allow fewer opportunities for the development of drug resistance.

Understanding the complex nature of ACT use is difficult, especially in the face of underlying drug resistance to partner drugs. Multiple ACT formulations and non-ACT therapies are currently being used around the world. This article briefly reviews recent advances in the monitoring of malaria drug resistance. It then discusses common ACTs and

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non-ACT therapies used to treat drug-resistant malaria. Finally, it reviews the urgent situation of artemisinin resistance on the Thai-Cambodian border and touches on new drugs that may be in the pipeline.

Advances in Antimalarial Drug Resistance Surveillance

The goal of antimalarial drug resistance monitoring has been to detect cases of treatment failure caused by drug-resistant parasites before they become widespread in the population and lead to increased morbidity and mortality. This is deceptively simple, because recurrent parasitemia in endemic countries can also result from a host of other factors including noncompliance, poor quality drug, inadequate drug levels, new infection (especially in areas of high transmission), and even varying levels of immunity to malaria. Traditionally, methods for measuring drug efficacy use a combination of in vivo clinical outcomes from treatment trials, in vitro drug susceptibility testing, and pharmacokinetic sampling. These methods have evolved over time and guidelines for determining in vivo therapeutic efficacy are now standardized by protocols published by the WHO [2]. Although not perfect, they provide a useful perspective on the parasite, drug, and host factors that may contribute to treatment failures. In the era of ACT, it has been more difficult to monitor drug efficacy, because it is difficult to decipher which part of a failing regimen is the problem. This topic was reviewed previously in this journal [3].

The use of molecular markers of drug resistance in recent years has added another dimension to surveillance efforts and generated insights into the global spread of drug resistance. Molecular markers have been identified for *Plasmodium falciparum* resistance to chloroquine (CQ), sulfadoxine and pyrimethamine (which together compose Fansidar; Roche, Basel, Switzerland), atovaquone-proguanil (Malarone; GlaxoSmithKline, Research Triangle Park, NC), and to a limited degree for various other antimalarials (Table 1). For CQ and sulfadoxine-pyrimethamine (SP), these involve single nucleotide polymorphisms (SNPs) in genes encoding a vacuolar membrane transporter protein and enzymes involved in folate synthesis, respectively. Parasites that have developed both CQ and SP resistance and subsequently develop resistance to a third operational drug are termed “multidrug-resistant.” Patients with an increased copy number of the *pfmdr1* (*P. falciparum* multidrug-resistance gene 1) encoding Pfgh1, a purported transporter pump, were found to have reduced responses to mefloquine, quinine, lumefantrine, and ACT combinations containing these drugs [4–6]. More recently, the *pfmrp* (multidrug resistance-associated protein) gene was associated with drug efflux in cultured parasites, and SNPs in the *pfmrp* gene were observed in recurrent infections following treatment with the ACT artemether-lumefantrine [7,8]. Finally, resistance to the atovaquone component of atovaquone-proguanil maps to the same locus that determines atovaquone resistance to *Pneumocystis carinii* [9].

Although using molecular markers for surveillance can be resource-intensive, and is often not predictive of clinical resistance in the individual patient, the potential to detect emerging trends of drug resistance before outright clinical failure makes them useful tools for policy makers preparing for drug policy change. Using molecular markers has also helped elucidate the geographic origins and historical spread of drug-resistant malaria. Genetic analysis of mutations in *pfcr1*, *dhfr*, and *dhps* and microsatellite markers flanking them have shown that resistant strains developed in a few loci then spread to other endemic areas [10,11•]. These analyses support the long-held theory that CQ-resistant parasites that first appeared along the Thai-Cambodian border in the 1950s and spread throughout Southeast Asia later migrated to East Africa in the 1970s, and spread throughout Africa by the 1990s. Likewise, it has been shown that pyrimethamine resistance generated near the Thai-Cambodia border in the 1960s evolved to highly resistant “triple mutant” types, then spread to other regions in

Asia and to Africa [12]. This origin of drug-resistant malaria strains in areas of relatively low transmission remains a curious paradox in malariology.

The availability of efficacious ACT and the push for elimination has led the WHO to now recommend that countries shift their antimalarial treatment policy to a new first-line regimen when treatment failures exceed 10%, and that a new drug being adopted as policy should have failure rates $\leq 5\%$ [13]. Efforts to collect and present drug efficacy data in a uniform format that permits comparisons are underway with the formation of a Worldwide Antimalarial Resistance Network (WWARN) [14]. The critical role for a worldwide surveillance system for drug-resistant malaria is undisputed in this age of increasing globalization.

Worldwide Drug-Resistance Patterns

Historically, Southeast Asia has been the center of the emergence of resistant malaria; however, few areas of the world are now impervious to the effects of drug-resistant malaria. Central America north of the Panama Canal and the Caribbean remain the only areas where CQ sensitivity is common. In South America, CQ resistance is widespread. Parts of the Amazon region have demonstrated high-level SP resistance and mefloquine resistance has been described, although not to the degree found in Southeast Asia [15]. In East and South Africa, high-level SP resistance is generally found. Comparatively, parts of West Africa still have relatively low levels of SP resistance. In Africa, amodiaquine (AQ) is generally more effective than CQ, but there is cross-resistance with CQ and the efficacy of AQ is also declining. South Asia and the Middle East also demonstrate SP resistance, but general sensitivity to mefloquine [16]. By the late 1990s and early 2000s, the absence of efficacious antimalarials led to the testing of combination therapies such as CQ+SP, AQ+SP, and chlorproguanil+dapsone. However, the success of combining two failing drug classes was predictably not high, and a new potent class of antimalarials was needed.

Rationale Behind ACT and Common Regimens

The antimalarial properties of the artemisinins and their derivatives—artemether, artesunate (AS), and dihydroartemisinin (DHA)—were discovered by the Chinese in the 1970s. However, it was not until the 1990s that their potency began to be appreciated by the rest of the world. By then, artemisinin monotherapies were widely available in Asia. The malaria community realized that to preserve this last class of efficacious antimalarials, a worldwide push for combination therapy would be needed. In 2001, the WHO recommended the use of ACTs in countries where *P. falciparum* malaria had developed resistance to the conventional antimalarials, citing its high cure rates and the potential to reduce the spread of drug resistance [17]. The number of countries that have adopted ACT as first-line therapy, as recommended by WHO guidelines published in 2006, has skyrocketed to 88 as of 2009, including every major country in Africa (Fig. 1) [18–21].

As with combination therapy for tuberculosis and HIV, the idea behind ACT is to achieve an increased barrier to resistance by using drugs with different mechanisms of action, forcing the parasite to develop multiple simultaneous mutations in order to become resistant. Because artemisinins typically achieve parasite reduction on the order of 10^8 -fold reduction within 3 days, but are eliminated from the blood within 1 to 3 h, they are generally paired with a partner drug that has a longer half-life and can “mop up” any remaining parasites [22••]. This allows shorter, 3-day regimens to promote adherence. On the other hand, in areas of high transmission, the “tail” of the longer-acting drug might promote the proliferation of drug-resistant parasites exposed to subtherapeutic levels of drug. Thus, for many reasons, it is essential that the partner drug still be effective in its own right, ideally achieving greater than 80% cure rates on its own. The futility of partnering an artemisinin

derivative with a drug with known resistance was dramatically shown by the failure of artesunate-CQ [23]. Currently, the WHO recommends the use of four common ACT combinations with a fifth, also generally accepted as being safe and effective (Table 2). In a recent Cochrane review that covered 50 head-to-head ACT studies, all five of the ACTs mentioned below achieved failure rates of less than 10% at most study sites, with notable exceptions [24].

Artesunate-Mefloquine

Artesunate-mefloquine (ASMQ), the first widely used ACT, was deployed on the borders of Thailand in 1994 in an effort to curb malaria with high levels of mefloquine resistance. This regimen remains generally effective in endemic areas in Thailand. Remarkably, malaria incidence at one site in northwestern Thailand fell 50% within 2 years of implementation of ASMQ and has continued to fall thereafter. This drop in incidence went beyond the effects of successful treatment and is believed to have resulted from a reduction in gametocyte carriage after treatment, making patients less infective to mosquitoes [25].

Currently, ASMQ is used in Cambodia, Thailand, and Myanmar and in some countries in South America. Its safety in African children and in pregnancy is under investigation. However, the long elimination half-life of mefloquine, approximately 2 to 3 weeks, makes it unsuitable for hyperendemic settings in Africa, where subtherapeutic drug levels for up to 3 to 5 weeks following treatment in the face of high rates of reinfection could quickly lead to drug resistance.

Artemether-Lumefantrine

The first ACT available in a coformulation was artemether-lumefantrine (AL) (Coartem; Novartis AG, Basel, Switzerland), which became available in 2004. Lumefantrine is related to mefloquine but has a shorter elimination half-life (4–5 days) and, importantly, has never been available as monotherapy. Against multidrug-resistant falciparum malaria, the six-dose regimen of AL was shown to be as effective as and better tolerated than artesunate-mefloquine [26]. Important exceptions to the widespread efficacy of AL are in western Cambodia and Uganda, where failure rates of about 15% have been reported [27,28]. In Kenya, frequent posttreatment reinfections have been correlated with genotypic markers of lumefantrine-resistant parasites [29].

AL has become the most widely used ACT in Africa, with more than 30 countries having adopted it as first-line therapy as of 2009 [19,21]. It is also the only ACT licensed in the United States. Remaining obstacles to achieving optimal outcomes include the more complex twice-daily dosing over 3 days, and the need for a fat-containing meal for optimal absorption, whereas most acutely ill patients have poor oral intake. Still, unsupervised dosing in Uganda and Malawi resulted in high cure rates of up to 98% [30,31]. There is increasing evidence that AL is safe in the second and third trimesters of pregnancy, though a longer course of treatment may be needed because of lower achieved plasma concentrations of artemether, dihydroartemisinin (DHA), and lumefantrine [32]. A dispersible formulation for babies has also proven highly effective in a study involving several African countries [33].

Artesunate-Amodiaquine

AQ (a 4-aminoquinoline like CQ) has activity against CQ-resistant strains, although there is some cross-resistance. Thus, in areas where CQ resistance is widespread, artesunate-amodiaquine (ASAQ) is not recommended. Efficacy of ASAQ varies in different regions of Africa, but is preserved where AQ monotherapy 28-day cure rates are greater than 80%. A coformulation is being deployed throughout western Africa. Although agranulocytosis,

neutropenia, and hepatitis have been associated with AQ prophylaxis in the past, they have not been described when AQ is administered in treatment doses [34]. Treatment is generally well-tolerated, though anecdotal reports exist of perceived intolerance because of unpleasant side effects. These side effects have led patients to not take AQ when it was co-blistered with artesunate [35]. Also, neutropenia has been found to be more common in HIV-infected than in non-HIV-infected children given AQ [36]. The lifespan of this ACT may be limited by rising CQ and AQ resistance.

Artesunate-Sulfadoxine-Pyrimethamine

As already discussed, some level of SP resistance is now widespread, but SP is a cheap, well-tolerated, single-dose drug with a relatively long elimination half-life. In areas where efficacy of SP remains greater than 80%, artesunate-sulfadoxine-pyrimethamine (AS-SP) has proven efficacious. The addition of AS also dramatically reduces gametocyte carriage, a known untoward effect promoted by SP monotherapy [37]. Because SP and other anti-folate drugs like cotrimoxazole will continue to be widely used in monotherapy form for intermittent prophylactic therapy during pregnancy and opportunistic infection prophylaxis in HIV patients, efficacy of this ACT combination is expected to erode over time. It was adopted as first-line therapy in India in 2007, and is also used in the Middle East and parts of South America.

Dihydroartemisinin-Piperaquine

Piperaquine is also a 4-aminoquinoline related to CQ. It has been used since 1978, mainly in China. It has a very long elimination half-life (4–5 weeks). DHA-PQ is well-tolerated, has once-daily dosing, and has shown excellent efficacy against multidrug-resistant strains in Southeast Asia with cure rates of 97% to 98% [38]. A recent Cochrane review covering 17 studies involving DHA-PQ concluded that it is at least as effective as ASMQ in Asia, and perhaps more effective than AL and ASAQ in Africa [24]. Despite being one of the more promising ACTs, it was not included in the 2006 WHO treatment recommendations because it had not yet been licensed under international good manufacturing practice. The coformulation has been commercially available in Asia as Artekina (Holleykin Pharmaceutical Co. Ltd., Guangzhou, China) and Duocotecxin (Beijing Holley-Cotec Pharmaceuticals Co. Ltd., Beijing, China) for some time, and is now also found in Africa. Recently, concern was raised that the dihydroartemisinin component is formulated at too low a dose in the combination pill, potentially compromising its field efficacy [39].

Many issues still need to be addressed if ACTs are to live up to their full potential and have an extended lifespan. Although coformulations are now readily available for some ACTs, they are not without drawbacks. In general, ACTs have a shorter shelf-life than non-ACTs. As a result, stringent regulatory agencies usually approve oral formulations of artemisinin-based combinations for shelf-lives of no more than 2 years. Efforts are underway to eliminate counterfeit and substandard drugs and to enforce the ban on marketing of oral artemisinin monotherapy. It was previously documented that 33% to 53% of artesunate tablets surveyed in the Mekong subregion were fake [40], although the percentage is believed to be much lower today. As with all therapies, health infrastructure and services must be improved to ensure not only that the drugs reach those who need them most, but also to avoid rampant overtreatment without evidence of parasitemia. Nowhere are these issues more relevant than in Africa. Finally, more safety studies in pregnant women, especially during the first trimester, and HIV-infected persons are needed. However, overall, ACTs are remarkably well-tolerated, and have become the mainstay of malaria therapy worldwide.

Non-ACT Treatments for Drug-Resistant Malaria

Although ACT is recognized as the best option for treating uncomplicated malaria, non-ACT treatments can still play a role in some instances. The most notable example is the combination of AQ and sulfadoxine-pyrimethamine (AQ-SP), which was a promising combination therapy before ACTs became more widely available. The long half-lives of the two component drugs allow it to reduce reinfection rates better than ASAQ or AS-SP. Results taken from four head-to-head studies against AS-SP in Africa showed it to be more efficacious, though AS-SP was predictably better at reducing gametocyte carriage [41]. Meanwhile, other ACTs were superior to AQ-SP in East Africa [24]. The WHO recommends this combination as an interim option where ACTs are not available and individual SP and AQ efficacy remains high (>80%).

Where ACT or other combination therapy is unavailable, oral quinine monotherapy is often the second-line treatment offered for uncomplicated malaria. Of the 41 African countries that have adopted ACT as first-line therapy, 29 of them use quinine as their second-line regimen (21). In reality, this means that quinine monotherapy is widely used. Through 2005, only sporadic reports of quinine failure had been reported from Southeast Asia, western Oceania, and Sudan. However, this likely does not reflect real-world efficacy because oral quinine is not well-tolerated—causing tinnitus, dizziness, and nausea—and also requires dosing three times daily. Thus, adherence to the 7-day regimen has always been questionable. A recent study in Uganda comparing its first-line AL to its second-line quinine regimen confirmed this suspicion, as quinine failure rates were significantly higher and correlated with poor compliance [42]. This has prompted calls for ACTs to be used as second-line treatment as well [43]. In Southeast Asia and South America, where quinine monotherapy is now ineffective, second-line treatment has been quinine and tetracycline for 7 days, with quinine monotherapy reserved for pregnant women.

Atovaquone-proguanil is a synergistic 3-day combination regimen that is reliably effective against multidrug-resistant malaria. It is well-tolerated and available as a fixed-dose combination. However, its high cost is prohibitive to large-scale deployment in resource-poor countries. Also, there is concern that resistance via cytochrome b-point mutations would emerge quickly under drug pressure. Given its effectiveness, however, it has been chosen for artemisinin resistance containment and *P. falciparum* elimination efforts on the southeastern border of Thailand with Cambodia [44].

Emerging Artemisinin Resistance

The rapid action of artemisinins and their rapid elimination from the plasma are theoretical built-in barriers to the development of drug resistance. However, reports of greater than 20% failure of ASMQ therapy from both sides of the Thai-Cambodian border first surfaced in the early 2000s [45•]. These reports generated great concern because no back-up drug for ACTs is currently available.

Because the hallmark of artemisinin therapy is a rapid parasite clearance time, and mefloquine is a more slow-acting drug, delayed parasite clearance times with ASMQ are thought to reflect declining artemisinin sensitivity. Data from ASMQ in vivo studies spanning more than a decade on the Thai border have shown increasingly slow parasite clearance. The percentage of participants parasitemic on day 3 (day 0 = day of initiation of therapy) increased from 0% in 1997 to 13% in 2007, with the odds of having parasitemia on day 3 increasing, on average, 32% per year [46]. Meanwhile, on the Cambodian side of the border, longitudinal in vitro drug susceptibility monitoring of more than 800 falciparum malaria isolates have demonstrated rising artesunate IC₅₀ values from 2001 to 2007 [47].

To sort out whether these ASMQ failures represented true clinical artemisinin resistance versus declining efficacy of the partner drug mefloquine, a series of trials using artesunate curative monotherapy were performed in western Cambodia. The strategy of using artesunate monotherapy effectively removes the partner drug as a variable. The three trials, carried out between 2006 and 2009, used different doses of artesunate varying from 2 mg/kg/d to 6 mg/kg/d for 7 days. The overall clinical outcomes were somewhat inconclusive, varying from 70% (14/20) efficacy in Pailin using 2 mg/kg dosing [48•] to ≥90% efficacy in the two consecutive trials in nearby Tasanh using both 2 mg/kg and 4 mg/kg dosing [49,50]. The high-dose (6 mg/kg) arm in Tasanh was halted before completion of enrollment because of observed neutropenia, but showed no impact of higher doses of artesunate on parasite clearance times or rates of failure [51]. Notably, these trials were conducted 3 to 5 years after the initial studies that documented ASMQ failures. During this period, there was a drop in *P. falciparum* malaria incidence and a change in the pattern of ACT use in western Cambodia, with a shift toward higher consumption of DHA-PQ, which has become widely available in the private sector.

The main finding from the three trials is that patients from Western Cambodia have slow parasite clearance times in response to artesunate therapy. In Pailin, it took patients a median of 3.5 days (~84 h) to clear their parasites. At least half of the patients in Tasanh took at least 3 days to achieve parasite clearance [50]. This is in contrast to the median 30 h of parasite clearance time found in Thai patients given oral artesunate in the 1990s [52]. This finding is important because the principal pharmacodynamic advantage of artemisinins is their accelerated clearance of young ring-stage parasites, preventing further maturation and sequestration of these parasites. Thus, the data suggest some degree of resistance to artemisinins among the parasites from this area.

The percentage of patients still parasitemic on day 3 has now been proposed as an *in vivo* marker of artemisinin resistance [53]. However, early detection of spreading artemisinin resistance would be greatly enhanced by the identification of a molecular marker of resistance. Efforts are underway to elucidate the genetics of artemisinin-resistant parasites by making use of isolates from the above trials and other isolates collected prospectively through the coordination of WWARN. Genome-wide studies and other molecular analyses are being applied in the hopes of identifying new candidate molecular markers, while also validating known and emerging markers that contribute to resistance [54].

Plans of malaria eradication were once thwarted by the emergence of CQ resistance originating along the Thai-Cambodian border. Fifty years later, there is no doubt that the emergence of artemisinin resistance from this same area would potentially have devastating consequences and once again threaten the substantial gains made in malaria control over the past few decades. In a prompt response, artemisinin resistance-containment activities have begun in this border region with the goal of eliminating *falciparum* malaria in the area. It is hoped that such efforts can be sustained long enough to achieve this goal.

Beyond ACT: New Drugs in the Pipeline

New antimalarials from diverse chemical groups and targeting different parasite stages are urgently needed that would allow implementation without concern for preexisting resistance. A review of new antimalarial drugs under development was published recently [55•]. Among them, pyronaridine-artesunate (Pyramax; Shin Poong Pharm. Co. Ltd., Seoul, South Korea) is a new ACT with single-tablet once-daily dosing for 3 days that represents a potential advantage over other ACTs in terms of compliance. Pyronaridine is a synthetic drug related to CQ, which does not exhibit much cross-resistance with CQ, quinine, or mefloquine. Phase 3 clinical trials of pyronaridine-artesunate in Africa and Southeast Asia

have been completed, and the application for drug approval will be submitted to the European Medicines Agency in early 2010.

Artemisone (Artemifone) is a semisynthetic artemisinin derivative. Its differing chemical structure from artemisinin may make it more effective against parasites on the Thai-Cambodian border. Plans are underway for a phase 2b trial where its effects on parasite clearance times will be evaluated. Finally, Rbx11160 (or OZ277) is a synthetic ozonide, which achieved only 60% to 70% clinical efficacy as monotherapy but achieved markedly improved efficacy when combined with piperazine. The combined formulation is now being moved into phase 3 clinical trials. The structural difference of Rbx11160 from semisynthetic artemisinins may also help target artemisinin-resistant strains.

Conclusions

The progressive evolution of antimalarial drug resistance has been a foregone conclusion. With all but a handful of countries having now adopted ACT as antimalarial drug policy, the development and spread of artemisinin resistance is widely feared. To prevent this from happening, a thorough understanding of the issues surrounding appropriate ACT use combined with strengthened monitoring of antimalarial resistance is needed. Only with these crucial efforts can we lengthen the lifespan of ACT and protect the gains made in malaria control in recent decades.

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Fig. 1. Number of countries adopting ACTs as first-line therapy by year, disaggregated by specific ACT drug. Each value marked indicates the cumulative number of countries having adopted the ACT by that year. The statistics shown are for policy adoption and do not necessarily represent policy implementation. *AL* artemether-lumefantrine; *ASAQ* artesunate-amodiaquine; *AS-SP* artesunate-sulfadoxine-pyrimethamine; *ASMQ* artesunate-mefloquine; *DHA-PQ* dihydroartemisinin-piperaquine. (Data from World Health Organization [18–20])

Table 1

Established molecular markers of antimalarial resistance

Drug	Year drug introduced	First reported resistance	Marker first described	Gene	Protein	Mechanism of resistance	Areas of substantial clinical resistance
Chloroquine	1945	1957	2001	<i>pfcr1^a</i>	PlCRT	Limited accumulation of CQ in the parasite digestive food vacuole	Everywhere except Central America (NW of Panama) and Caribbean
Pyrimethamine			1996	<i>dhfr</i>	Dihydrofolate reductase	Reduced binding affinity to antifolate	Southeast Asia, East and Central Africa, Amazon
Sulfadoxin e	1967	1967	1997	<i>dhps</i>	Dihydropter oate synthase	synthesis enzymes	region of South America
Mefloquine	1985 ^b	1989 ^c	2004	<i>pfmdr1^d</i>	Pgh1	Drug transporter pump	Thai-Myanmar border, Thai-Cambodian border, Amazon region
Atovaquone	1996	1996	2000	<i>cytb</i>	Cytochrome b	Affects binding to parasite mitochondrial cytochrome complex	None

^a Also associated with amodiaquine resistance

^b First introduced for field trial in 1977, adopted as first-line drug by Thai National Malaria Control program in 1985

^c A single case of resistance was confirmed in a clinical trial in 1982; resistance emerged on the Thai-Cambodian border in 1989

^d Also associated with resistance to quinine, lumefantrine, halofantrine, artesunate, and amodiaquine

Table 2

Common artemisinin-based combination therapies and coformulations

Artemisinin component	Partner drug	Coformulation	Elimination half-life of partner drug	Areas where ACT is commonly deployed
Artesunate	Mefloquine	ASMQ (Far-Manguinhos Institute of Pharmaceutical Technology, Brazil)	2–3 wk	Southeast Asia, South America
Artemether	Lumefantrine	Coartem (Coartem; Novartis AG, Basel, Switzerland)	3–4 d	Africa, South Asia, Middle East, South America
Artesunate	Amodiaquine	ASAQ	~10 d	West Africa
Artesunate	Sulfadoxine-pyrimethamine	None	3–7 d	South Asia, Middle East, South America
Dihydroartemisinin	Piperaquine	Artekin (Holleykin, Guangzhou, China); Duocotecxin (Beijing Holley-Cotec, Beijing, China); Eurartesim (Sigma-tau Industrie Farmaceutiche Riunite S.p.A., Rome, Italy)	4–5 wk	Southeast Asia, China, Africa

ACT artemisinin-based combination therapies; ASAQ artesunate-amodiaquine; ASMQ artesunate-mefloquine