Published in final edited form as:

Curr Opin Pediatr. 2010 December ; 22(6): 798–803. doi:10.1097/MOP.0b013e328333fac44.

Treating uncomplicated malaria in children: comparing artemisinin based combination therapies

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Abstract

Purpose of review—In response to increased resistance to conventional drugs, the WHO is promoting artemisinin-based combination therapy (ACT) for treating uncomplicated malaria. The objective of this report is to review the available evidence on the efficacy and effectiveness, acceptability, and deployment of ACT in resource limited settings with a focus on Sub-Saharan Africa.

Recent findings—ACTs are very effective in the treatment of uncomplicated *Plasmodium falciparum* (*P. falciparum*) malaria in children. ACTs are relatively safe and tolerable with no reported resistance in Sub-Saharan Africa despite indications of delayed clearance of infections in South East Asia. The major challenges to the widespread use of ACT include its high cost, availability, and inefficient delivery due to among others weak health care systems.

Summary—ACTs are an essential tool in the fight to control and eliminate malaria. They are currently the most effective drugs against *P. falciparum* malaria. They should be deployed through programs that address availability, cost, adherence, and quality assurance. Initiatives including home based management of malaria, improving public sector procurement and supply chains, and reducing private sector pricing should make ACTs more accessible for Sub-Saharan African children who bear the brunt of the burden of malarial disease.

Keywords

Malaria; Artemisinin-based combination therapy; Home based Malaria Management; Malaria Diagnostics

Introduction

In response to increased resistance of malaria parasites to conventional drugs, the WHO has been promoting for the past decade artemisinin-based combination therapy (ACT) for treating uncomplicated malaria[1**]. ACTs are now being used in over 150 malaria endemic countries. The recommended combinations are artemether-lumefantrine (AL), artesunate-amodiaquine (AS+AQ), dihydroartemisinin-piperaquine (DP), artesunate-mefloquine (AS+MQ), and artesunate-sulfadoxine-pyrimethamine (AS+SP) the first four available as co-formulations or fixed dose combinations. The choice of an ACT in a country or region should be based on the level of resistance of medicine partner to the artemisinin component

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in the combination[2**]. Other factors to consider are acceptability, safety, tolerability, ease of adherence, availability, co-formulation, and cost[1**,2**].

Efficacy and Effectiveness of ACT

Artemisinin, originally isolated from the Chinese wormwood *Artemisia annua*, is extremely potent against chloroquine (CQ) and sulphadoxine–pyrimethamine (SP) resistant *P. falciparum*. It clears malaria parasites faster than other anti-malaria drugs[3*]. Its three bioavailable semi-synthetic derivatives, artemether, artusunate, and dihydroartemisinin, have short half lives and are combined with longer acting antimalarials to form the most effective anti-malaria drugs currently available[1**,2**,3*]. ACTs have higher cure rates, faster parasite clearance and decreased gametocyte carriage compared with monotherapy[1**,2**,3*].

Artemether-lumefantrine is the first fixed-dose ACT regimen to be manufactured under Good Manufacturing Practice conditions. It is the most widely adopted ACT regimen in African malaria control programs. AL is approved for the treatment of uncomplicated malaria in adults, children and infants, and in non-immune travelers. AL is efficacious for treating uncomplicated malaria in children and the frequency of associated adverse events is not higher than other available ACT regimens[4*]. AL demonstrates cure rates above 90%, even in areas of multiple drug resistance[2**,5,6,7]. After its introduction, over 250 million treatments of AL have not revealed any new safety concerns apart from hypersensitivity and allergies, known class effects of artemisinin derivatives[8*]. The most common regimen is a three day twice a day dosing scheme; administration recommended with fatty food necessary to assist lumefantrine absorption.

Results from Africa indicate that combinations of AS + AQ and AS + SP are highly effective, although efficacy may be compromised in areas with moderate to high levels of resistance to SP and AQ. In randomized comparative trials, the crude efficacy of AS+AQ was 75.9% [9**]. AS+AQ compares well to other treatments and meets the WHO efficacy criteria for use against *P.falciparum* malaria in many, but not all, the sub-Saharan African countries where it was studied[9**,10,11]. A new fixed-dose combination is safe and efficacious even in children under 5 years of age. A once-a-day intake of this new combination appears effective in the treatment of uncomplicated *P. falciparum* malaria both in adults and children [12**]. Concerns have been raised about the possibility of neutropenia in patients following repeated treatment with amodiaquine containing combination. One study in Uganda found an increased rate of neutropenia in HIV infected children treated for malaria with AS+AQ [13].

DP has proved to be a safe, well tolerated, and highly effective treatment of *P.falciparum* malaria in Asia and Africa with efficacy over 95%[14*,15*]. DP is as efficacious as AL in treating uncomplicated malaria in African children from different endemicity settings, and shows a comparable safety profile[16**]. It has an added advantage because it has a longer post-treatment prophylactic effect[16**]. Other studies have similarly shown high efficacy with dihydroartemisinin piperaquine. The drug is well tolerated with no obvious drug associated adverse events[17,18,19]. The treatment efficacy of 3 different ACT regimens from a series of randomized clinical trials conducted in different transmission settings in Uganda is shown in table 1. The results show that DP was superior to AL and AQ+AS for reducing the risk of recurrent parasitemia and recrudescence. DP thus appears to be a good alternative to AL and AQ+AS as first-line treatment of uncomplicated malaria in Uganda.

ACTs containing slowly eliminated partner drugs such as piperaquine or mefloquine exert a greater post treatment prophylactic effect against additional infection and relapse compared to more rapidly eliminated partner drugs, such as lumefantrine [17,20]. The clinical benefit

of this transient additional protection lies in delaying the next recurrence. Patients have longer periods free of symptomatic malaria, allowing a greater time for hematologic recovery, which in turn reduces the cumulative risk of anemia, an important cause of malaria morbidity [20]. On the other hand, prolonged exposure to long acting partner drugs could lead to the development of resistance blunting the long term effectiveness of a subclass of ACTs.

Treatment with ACTs significantly reduces infectiousness of individual patients with uncomplicated *P. falciparum* malaria[3*,21]. They are more effective against gametocytes than previous first-line antimalarials and therefore have the potential to reduce parasite transmission. ACTs have the potential for transmission reductions approaching those achieved by insecticide-treated nets in lower-transmission settings[22]. Eliminating the source of transmission by mass treatment of human populations in malaria-endemic areas using an ACT and primaquine has been experimented in Cambodia and reduced parasite rates from 52.3% to 2.6% after three years[23**].

Acceptability of ACT

Parental perceptions of the efficacy and side-effects of ACT regimens have been favourable. In Tanzania, community members spoke favourably of ACTs emphasizing their ability to help children to rapidly recover from malaria, without undesirable side-effects [24]. Similarly in Ghana, a majority of parents reported an increase in rapidity of symptom resolution, compared to their previous experience of other childhood malaria therapies, and to parents of children treated with monotherapy [25]. Major interrelated factors that still affect acceptability among the poorest populations are poor provider patient relationship, unmet patient expectations, alternative illness causation beliefs, perceived poor effectiveness of treatment, and distrust in the quality of care [26]. Continued education of communities about malaria prevention, diagnosis and treatment is vital.

Health worker acceptance of ACTs is also important. Changing clinical practice requires more than the adoption of ACT regimens as first line therapy by national malaria control programs. Evaluations of adoption of new ACT based national malaria guidelines in Kenya, Zambia, and Uganda demonstrated improved, but less than optimal adherence to ACT guidelines [26,27,28,29,30,31]. Health workers knowledge and attitudes, the availability of malaria diagnostics and drugs, and the balancing of concurrent medical conditions are just some of the factors that may lead clinicians to prescribe alternative treatments [26,27,28,29,30,31,32,33]. More effort is needed to inform healthcare workers and to provide them with the resources necessary for effective malaria case management.

Access to ACT

For effective treatment to reach greater numbers of people in need, the distribution of ACTs should be supported in ways that respond to specific needs of individual countries. The models currently proposed to achieve improved ACT distribution include scaling up public sector provision of health care and subsidising drugs provided through the private sector.

ACTs should be available at a cost that every family can afford and close enough for any sick person to obtain promptly. By 2009, 77 of 81 malaria-endemic countries and territories had adopted ACTs for use in their national drug policy (Fig. 1). Sixty countries are deploying these medicines in the general health services, with varying levels of coverage [34*]. Access to ACTs is poor in African countries with less than 15% of children under 5 years of age receiving an ACT when they have fever [34*].

In many malaria endemic countries, weak and/or poorly distributed public health systems and inconsistent supply chains limit access to ACT via the public sector. Similarly, private sector pricing of ACTs is currently too high for most families in sub-Saharan Africa to afford.

Other challenges in the ACT era

National malaria control and elimination programs face many challenges in providing ACT including increasing the use of malaria diagnostics, integrating ACT in home management of malaria (HMM), addressing the lack of effective second line therapy, and providing appropriate pediatric drug formulations.

Malaria diagnostic testing

Malaria diagnostic testing is increasingly advocated in resource limited settings to promote cost effective use of ACTs. The WHO 2010 malaria treatment guidelines recommend parasitological confirmation either by microscopy or RDTs whenever possible [1**]. However, the proportion of patients treated for malaria who have a confirmed diagnosis is still low in Africa compared with other regions of the world. Consequently, anti-malarials are commonly used to treat patients without malaria [35*]. The continued presumptive treatment of fever in areas of decreasing malaria transmission leads to missed or delayed diagnosis of the true underlying disease, unnecessary costs due to overtreatment with expensive ACTs, and may contribute to the spread of resistance. While there have not been reports of ACT resistance in Africa, in vivo reduced susceptibility to artesunate has been reported in Cambodia [36*]. Increasing access to diagnostic testing is a necessary step in providing successful disease management in malaria-endemic areas [32].

Home malaria management (HMM)

In areas with high malaria transmission and limited access to health facilities, home malaria management, in which families receive anti-malarials to presumptively treat febrile illnesses, has played an increasing role in malaria control efforts[37*]. Implementation research is needed to develop appropriate HMM strategies in the ACT era[37*].

Provision of ACT at the community level has increased access to high risk groups living in underserved areas. A multi-country study in Ghana, Nigeria and Uganda, showed that the proportion of febrile children who received prompt treatment and the correct dose for the assigned duration of treatment ranged from 71% to 87%[38]. The use of RDTs, through community health workers, in the context of HMM has been studied in a number of settings. The cost-effectiveness of a 'test-and-treat' strategy for the home-based management of malaria (based on an artemisinin-combination therapy) was compared with that of a 'treat-all' strategy in an area of high malaria transmission in southern Mali[39*]. Use of RDTs was not cost-effective compared with the presumptive treatment of malaria with an ACT [39*].

By contrast, a randomized trial of ACT based HMM without diagnostic testing in the capital of Uganda, found that HMM led to significant over treatment, higher costs and only modest health benefits[40**]. The authors concluded that HMM without diagnostic testing may not be appropriate for urban areas with significant access to health facilities and fairly low malaria transmission[40**]. Furthermore, in Sudan, the use of RDTs improved the level of accuracy and trust in the diagnosis; however 30% of volunteers did not rely on the negative RDT results when treating fever cases [41]. These studies suggests that the appropriate approach to HMM will need to be tailored to local conditions and that one size fits all policies are unlikely to work, even at the national level.

Second line therapy

The WHO recommends alternative locally effective ACT regimens and seven days of artesunate or quinine plus tetracycline, doxycycline, or clindamycin as second line therapies for *P. falciparum* malaria[1**]. Most sub-Saharan African countries have trouble maintaining adequate supplies of one recommended ACT and do not have adequate supplies of tetracyclines nor clindamycin. Therefore, many countries currently recommend quinine monotherapy as second line therapy[42**]. In these countries, providers faced with low supplies of ACTs use seven day courses of oral quinine monotherapy as a first line alternative for uncomplicated malaria[42**].

A recent randomized control trial comparing AL to quinine monotherapy was stopped due to clear superiority of AL (cure rate 96% vs. 64% for AL and quinine respectively hazard ratio 10.7 95% CI 3.3-35.5 $p=0.001$)[42**]. The authors found significantly higher rates of non-adherence for the seven day quinine regimen compared to the three day AL regimen[42**]. This study highlights the lack of an appropriate policy for second line drugs for the treatment of uncomplicated malaria in much of Sub-Saharan Africa. There is an urgent need to strengthen and broaden drug supplies to include the requirements for second line treatment [43]. In addition, as quinine is widely available throughout sub-Saharan Africa, providing the appropriate partner drugs would also provide effective second line therapy [44].

Paediatric formulations of ACT's

Administering ACTs to infants and small children can be difficult and time consuming. Specially formulated anti-malarials for this vulnerable population is vital to ease administration and help ensure that an accurate dose is received. Most anti-malaria tablets need to be crushed and mixed with water or food for infants and young children. They have a bitter taste, which may result in children spitting the medicine out and not receiving the full therapeutic dose. Dispersible AL was developed and has shown excellent efficacy, safety and tolerability[45*]. Easing administration may foster adherence, improving therapeutic outcomes in infants and young children and preserving the efficacy of ACTs[45*,46].

Conclusion

ACTs are an essential tool in the fight to control and eliminate malaria. They are currently the most effective drugs against *P. falciparum* malaria. They should be deployed through programs that address availability, cost, adherence, and quality assurance. Initiatives including HMM, improving public sector procurement and supply chains, and reducing private sector pricing should make ACT more accessible. Further implementation research is needed on new approaches for the large-scale deployment of ACTs. In addition more basic and clinical research is needed to search for cheaper and more effective therapeutic agents.

Acknowledgments

Supported in part by an Institutional Research Training Grant (T32MH019105) from the National Institute of Mental Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Mental Health or the National Institutes of Health.

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Figure 1. Adoption of policy and deployment of artemisinin-based therapy (ACT) by year, global data, 2001–2008

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Table 1

Antimalarial drug surveillance in Uganda 2003 to 2008

Year and reference	Study site	Duration of follow-up	Treatment arms*	Number enrolled	Risk of treatment failure	
					Unadjusted by genotyping	Adjusted by genotyping
2003	Kampala	28 days	CQ+SP	132	60%	40%
			AQ+SP	134	18%	9%
			AQ+AS	134	18%	3%
2003	Jinja	28 days	CQ+SP	168	63%	39%
			AQ+SP	186	29%	13%
			AQ+AS	189	19%	4%
2004	Apac	28 days	CQ+SP	185	67%	25%
			AQ+SP	183	37%	7%
			AQ+AS	174	54%	11%
2004	Tororo	28 days	CQ+SP	166	88%	37%
			AQ+SP	181	61%	19%
			AQ+AS	194	75%	13%
2004	Arua	28 days	CQ+SP	180	87%	51%
			AQ+SP	180	53%	14%
			AQ+AS	174	51%	8%
2005	Tororo	28 days	AQ+AS	204	66%	4%
			AL	204	52%	7%
2006	Kampala	28 days	AQ+SP	253	26%	14%
			AQ+AS	232	17%	5%
			AL	202	7%	1%
2006	Apac	42 days	AL	210	53%	16%
			DP	211	43%	7%
2007	Kanungu	42 days	AL	199	33%	6%

Year and reference	Study site	Duration of follow-up	Treatment arms*	Number enrolled	Risk of treatment failure	
					Unadjusted by genotyping	Adjusted by genotyping
2008	Tororo	28 days	DP	215	12%	2%
			AL	320	35%	1.0%
			DP	315	11%	0.3%