

From famine to feast: the transformation of the ACT malaria treatment landscape since 2004

Medicines for Malaria Venture and Drugs for Neglected Diseases initiative explore the advantages of multiple ACTs for malaria and how to prolong their usefulness

'As doctors, we want to use effective treatments. We cannot continue prescribing a first-line malaria treatment – such as sulfadoxine-pyrimethamine - which we know is not going to cure the patient.'

Médecins Sans Frontières, 2002

As little as 10 years ago, owing to drug resistance, a clinician treating a patient for malaria would be routinely confronted with a terrible dilemma: 'Will the drug I prescribe actually cure my patient?' Between 1999 and 2002, rates of resistance to chloroquine and sulfadoxine-pyrimethamine (SP) in excess of 90% and up to 60%, respectively, were being reported in parts of East Africa.¹ This dire situation continued until World Health Organization's (WHO) prequalification of the first artemether-lumefantrine (AL) artemisinin combination therapy (ACT) in 2004, followed by growing support from donors for the large-scale introduction of ACTs. By 2005, 40 countries had adopted ACT² as either first or second-line therapy and their distribution broke through the 10 million treatment mark and steadily increased over the next eight years, spurred on by the development of new fixed-dose combinations.

By 2012, 79 countries and territories had adopted ACT as first-line treatment for uncomplicated malaria.³

Almost 200 million ACTs were procured for use by public health systems in 2013, with around another 150 million treatments procured for use in the private sector, primarily in price-subsidised schemes.⁴ WHO guidelines today recommend the use of five different ACT options, four of which are available in fixed-dose combination - strongly preferred by WHO over co-blistered combination therapies, as they 'promote adherence to treatment and reduce the potential selective use of the medicines as monotherapy.'⁵ This dramatic increase in the availability and diversification of treatment options represents a unique moment in the history of malaria treatment. While there are worrisome signs of the limited spread of artemisinin resistance in the Greater Mekong sub-region in Southeast Asia, there is no sign yet of artemisinin resistance in Africa.⁶

Accordingly, African countries may be able to rely on these effective medicines for several years to come.

Combination**	Manufacturer(s) and year prequalified or SRA-approved*	Fixed dose (FDC) or loose
Artemether-Lumefantrine (AL)	Novartis (2004-tablet; 2009-dispersible)	FDC
	Ajanta (2008-tablet; 2012-dispersible)	FDC
	Ipca (2009-tablet)	FDC
	Cipla (2009-tablet)	FDC
	Strides (2013-tablet)	FDC
	Macleods (2013-tablet)	FDC
	Mylan (2014-tablet)	FDC
Artesunate-Amodiaquine (AS-AQ)	Guilin (2007-co-blistered, 2012-FDC)	FDC
	Sanofi (2008)	FDC
	Ipca (2008-co-blistered; 2012-FDC)	FDC
	Ajanta (2013)	FDC
	Strides (2011)	Co-blistered
Cipla (2008-co-blistered; 2014-FDC)	FDC	
Dihydroartemisinin + Piperaquine (DHA-PQP)	Sigma Tau (2011)*	FDC
Artesunate + Mefloquine (AS-MQ)	DNDi / Cipla (2012)	FDC
Artesunate + [Sulfadoxine + Pyrimethamine] (AS-SP)	Guilin (2012)	Loose
* SRA: Stringent Regulatory Authority; EMA marketing authorisation; FDC: Fixed Dose Combination		
** Not listed: Pyronaridine Artesunate, by Shin Poong Pharma. While this drug has been granted a positive scientific opinion by the EMA Article 58 review process and is listed on WHO's prequalified drug list, the drug is not yet included as a recommended treatment in the WHO Standard Treatment Guidelines.		

Table 1. WHO-recommended ACT treatments for uncomplicated malaria.⁷

Today, there are five distinct combinations of partner drugs with artemisinin (Table 1). This comparative diversity of ACTs confers multiple advantages for global strategies to combat malaria:

(a) Differentiated use of ACTs for complementary interventions. While all the ACTs listed have been developed to treat uncomplicated malaria, in the past three years there has been a growing interest in additional therapeutic interventions as part of national malaria control programming. For example, to avoid lighting the fire of drug resistance to medicines used for treatment, several countries have selected a different ACT for mass drug administration or chemoprevention studies than is used for treatment.^{8,9,10}

In the Sahel region, seasonal malaria chemoprevention (SMC) is currently being scaled-up. SMC uses a loose combination of SP+Amodiaquine (AQ) rather than an ACT but, in areas where it is deployed, WHO states that alternative antimalarials containing neither SP nor AQ must be used for the treatment of uncomplicated malaria.¹¹ Thanks to the availability of alternative ACTs for uncomplicated acute malaria, SMC offers the potential to save thousands of children's lives in West Africa.

(b) Increased patient/provider choice and adaptation for patient sub-populations. Having several quality treatment options is not only a boon for healthcare professionals but also for patients, who often buy their medicines from private drug sellers where they select which ACT to take. As such, increasing the choice of quality medicines available in the private sector may improve the likelihood that an effective ACT will be selected.

Although all of the ACTs listed are considered effective for uncomplicated malaria, formulation and dosing differences may make some more useful for specific sub-populations. For example, a pleasant-tasting dispersible paediatric formulation or a single daily dose versus a twice a day treatment may be particularly well suited to a rural/community delivery programme where thinly spread healthcare workers may not be able to monitor treatment adherence.

(c) Strengthening options for alternative first- and second-line treatments for uncomplicated malaria. Sometimes, for unclear reasons (e.g. incomplete dosing), a patient is not completely cured after a course of treatment. Given the potentially life-threatening nature of the infection, healthcare workers must determine, with imperfect information, if a second round of treatment is necessary. In this situation, it is critical to have an effective second-line course of treatment.

(d) Diversifying first-line treatment options through different supply chains. In 2007, Ghana pioneered a national malaria treatment policy that *de facto* embraced the concept of multiple first-line therapies' (MFL).¹² Three different ACTs (AL, DHA-PQP, AS-AQ) were approved as interchangeable first-line medicines for the treatment of uncomplicated malaria. In practical

terms, Ghanaian officials determined that the public sector system would dispense AS-AQ and AL, and that private sector outlets would offer patients DHA-PQP as the third approved ACT option. Today, as more countries are registering prequalified versions of different ACTs, their ability to explore variations on the Ghanaian experience becomes more feasible.

(e) Enhancing stock security through a diversified base of suppliers. Public health planners generally prefer to have multiple options for the manufacture and supply of essential medicines worldwide. Reliance on one or two manufacturers creates vulnerability for the global supply chain, as any disruption for a single company can become a global public health crisis. Diversification in supply not only diminishes the chances of major disruptions in the supply chain but also, thanks to increased competition, can help to increase drug affordability.

(f) Keeping resistance at bay. While African countries should be able to count on continued efficacy of today's ACTs for many years to come, at some point, artemisinin resistance will emerge and spread. WHO's recommendations for parts of Southeast Asia¹³ have included switching between different ACTs in areas of identified drug resistance in recent years. Thus, it may be that having a wide variety of ACT combinations today will help buy time when resistance comes knocking in Africa.¹⁴

The way forward

Today's global pharmacopeia for uncomplicated malaria contains more therapeutic options than at any point in history. Today, WHO recommends five distinct ACT combinations. With the potential broader introduction of pyronaridine-artesunate as a new ACT in 2015-2016, that figure could rise to six. It is a remarkable time.

Continuing technological advances - such as the shift towards semi- and fully-synthetic artemisinins to reduce dependence on agriculture, and the likely introduction of single-dose cures in the next few years - will help contribute to the eventual elimination of this human scourge. Meanwhile, to prolong the usefulness of ACTs, key areas for action include:

1. Exploring new ways to utilise today's wide range of ACTs. For example, countries could choose to emulate the example of Ghana in rolling out MFL adapted to their settings.
2. Continuing to document and publish evidence from modelling and simulations that may build stronger evidence regarding how to optimally use an increasing array of anti-malarial medicines.
3. Constant monitoring for signs of emerging drug resistance; the earlier it can be detected, the sooner an informed decision can be made to switch to an alternative ACT. The discovery of a molecular marker of artemisinin resistance is an important breakthrough in helping ensure the longevity of this drug class¹⁵ and new tools should allow reductions in parasite susceptibility to be detected earlier.¹⁶
4. Maintaining a global focus on addressing the manufacture and distribution of counterfeit and sub-standard ACTs - fake medicines threaten patient health and accelerate the decline of the ACT class of therapies.

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Conclusion

Almost 10 years ago, African countries began a major transformation of malaria treatment protocols in favour of ACTs, turning away from failed treatment regimens based on SP and chloroquine. Since then, ACTs have contributed enormously by providing fast and effective cures for uncomplicated malaria, with over 1.5 billion treatments distributed.² Given the approximate 95% efficacy of WHO-prequalified ACTs in providing a complete cure for uncomplicated malaria, the life-saving impact of ACTs has been massive.¹⁷

In the future, the next therapeutic revolution will be simpler, single-dose cures for malaria. Until then, the wealth of ACTs available today should continue to serve the evolving needs and demands of African malaria control programmes with greater versatility than has ever been possible in the history of malaria control. Wise drug policies can preserve the efficacy of the ACTs throughout Africa and beyond, and can ensure an effective arsenal of these medicines for many years to come.¹⁸

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Someone else's problem?

Antibiotic resistance has shot to prominence again with a major focus being called for by British Prime Minister, David Cameron. The story is of course not new, and I can recall articles on the subject that we've carried in this journal dating back to certainly the early 1990s if not before (alas we don't have a definitive index... so difficult to search other than manually for the pre computer revolution editions!).

The 'international charge' is that the professions prescribe badly, the consumers are sub-compliant in consumption; and Big Pharma doesn't prioritise the sector because selling a product that is used in

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