Malaria Treatment: ACT Two

An influx of money and a new generation of drugs called artemisinin-based combination therapies (ACTs) are raising optimism that malaria’s toll can be reduced

KUNKURA KEBELE, ETHIOPIA—Fanta Dargie and his family live in a modest mud hut, furnished with little more than a table, a few chairs, two hammocks, and some shelves holding the basic necessities for life in Ethiopia’s poor countryside. And yet, he’s on the forefront of a medical revolution.

Hidden in a corner on the dusty floor of Dargie’s hut, in a hamlet 450 kilometers north of Addis Abeba, is a white box the size of a photocopier. After opening a minuscule padlock, Dargie shows the contents: blister packages containing the latest generation of malaria drugs. Rummaging through the box, he also pulls out dozens of simple diagnostic tests, each smaller than a cigarette lighter, as well as rubber gloves, some pens, and meticulously filled-out patient forms.

Every morning before Dargie goes to work, people from his and surrounding villages can come see him if they, or their children, have a fever. He will draw a drop of blood and test it for the presence of *Plasmodium falciparum*, the deadliest malaria parasite, a procedure that takes just minutes. If the test is positive, he can immediately give the patients free pills to take home, along with simple instructions on how to use them.

Dargie, a farmer who volunteers as a “community health worker,” knows all about the importance of the drugs distributed in this study. He lost two children to malaria. “I don’t want that to happen to other people,” he says.

Many people ask why it has taken so long. The new generation of drugs, called artemisinin-based combination therapies (ACTs), has been around for a decade. They’re effective and easy to use, and they cost less than $2 for a potentially lifesaving 3-day treatment course. And yet, a shortage of money, a lack of political will, and logistical problems have long prevented the drugs from reaching those who need them—especially in Africa, where malaria kills an estimated million people a year.

Not any more. Money to buy the drugs has started pouring in through agencies such as the Global Fund to Fight AIDS, Tuberculosis, and Malaria. Affected countries have become serious about introducing ACTs, and they are coming up with new ways—such as the pilot project Dargie is participating in—to bring them almost to the patient’s doorstep. These fine-grained distribution systems are a logistical puzzle—but they’re crucial, because a child can die from malaria within 24 hours of the onset of the first symptoms. Meanwhile, an unprecedented new plan to serve private markets through a “global subsidy” may see the light of day next month.

This new push to introduce ACTs—along with the massive distribution of insecticide-treated bed nets (see p. 557)—is giving many malaria fighters hope that, after years of failures and broken pledges, they may finally be on the cusp of making a significant dent in the disease’s toll. The experience in places such as Zanzibar, where new data suggest malaria transmission has collapsed, has given them hope that results may come fast as well.

“We do get real, perceptible, stunning results,” says Kamini Mendis of the World Health Organization (WHO) in Geneva, Switzerland. “I really think we are in a good position now,” adds Nicholas White, a malaria
An old new weapon

Artemisinin is a compound derived from *Artemisia annua*, or sweet wormwood, a plant that has long been known to help fight fever in China. After groundbreaking Chinese studies in the 1970s, the compound made its way to Western labs in the 1980s. Along with a small slew of chemical relatives, it was found to be highly effective against *Plasmodium*, and despite widespread use, especially in Asia, there have been few signs of resistance in the malaria parasite. To keep it that way as long as possible, experts agree that the drugs should always be taken with another, existing malaria drug. Hence the combination therapies.

But as the evidence of their efficacy grew—and older drugs such as chloroquine and sulfadoxine-pyrimethamine became increasingly useless—patients still weren’t benefitting. “I think we were naive to think that evidence would naturally translate into new policies,” White says. “It does in rich countries. But in Africa, mothers who lose their child don’t come banging on the doors of Parliament.”

Money was long a key problem, but so was institutional inertia. Compared with older drugs, which cost a dime or less per treatment course, the cost of ACTs was prohibitive for many African governments. Although WHO officially started advocating ACTs in 2001, it didn’t push hard enough for the switch, says White.

A vast partnership called Roll Back Malaria (RBM), launched to much fanfare in 1998, also proved a disappointment. Comprised of almost every organization or agency involved in malaria, RBM went through one leadership change after another and ended up in turf battles with WHO; meanwhile, a set of ambitious targets set in the Nigerian capital Abuja in 2000—including the plan to halve the malaria burden by 2010—were going nowhere. “There was too much talk, and endless meetings, but no action,” White says.

Donor countries and the Global Fund, too, have come under fire for not acting swiftly enough. Leading the criticism has been Amir Attaran, a Canadian law professor and immunologist, who, with others, accused the fund and WHO of “medical malpractice” in an article published in the 17 January 2004 issue of *The Lancet*—a charge that the organizations say was unfair and based on inaccuracies, but which they also recognize as having helped speed change.

Meanwhile, there were problems with the supply of artemisinin as well. The compound is extracted from *A. annua* plants, grown mostly on farms in China and Vietnam that had trouble keeping up with the booming demand. Researchers are working to synthesize the compound or make *Escherichia coli* churn it out (*Science*, 7 January 2005, p. 33), but this is expected to take at least another 5 years.

The landscape looks very different today.

Donors are pushing ACTs, and a United Nations Children’s Fund (UNICEF) report issued last week showed that all but a few African countries have switched their policies—at least on paper—to make ACTs the standard treatment. Although long-term worries about the artemisinin supply remain, the price has come down sharply. Pharmaceutical companies have started mass-producing four WHO-recommended ACTs, and the Medicines for Malaria Venture (MMV) in Geneva, Switzerland, has three more combinations in phase III clinical trials. Many say RBM is working better since the latest reform, 2 years ago.

But the biggest change has been the increasing political attention and the new money. Few would have predicted 10 years ago that a U.S. president would celebrate Africa Malaria Day—and do a goofy dance with a West African dance company—at the White House, as President George W. Bush did last May. (“I think I made his day by saying the European Union should do the same,” says MMV President Chris Hentzschel, who attended the event.) The Global Fund is flush with cash, and other funds—such as Bush’s 5-year, $1.2 billion President’s Malaria Initiative and UNITAID, paid for by a tax on airline tickets in eight countries—have also begun disbursing money.

As a result, more than 100 million ACT treatment courses found their way to patients in 2006, up from just 3 million in 2003. Some 63 million of those were a combination of artemether and lumefantrine, produced by Novartis under the brand name Coartem; the company is making more of it than any company has ever produced of any drug, a Novartis spokesperson says.

That doesn’t mean there aren’t still major problems. One hundred million is less than one-fourth of the number of malaria treatments taken worldwide every year. And the UNICEF report shows that in 14 sub-Saharan countries for which good data were available between 2004 and 2006, Zambia provided just 13% of febrile children with ACTs; all the others scored less than 6%. (The numbers are expected to be much higher in the next survey.)

Procedures to apply for the drugs through the Global Fund are complicated and lengthy, says Mendis; many countries saw their proposals rejected in the fifth and sixth round of funding. Because countries often apply with integrated control plans, ACT delivery can suffer if, for instance, a country’s bed-net strategy is judged insufficient. RBM and other organizations are helping countries put together better proposals for the current, seventh round.

But even when the drugs arrive, the logistics of distributing them are often difficult. Several ways to change that are on display in Ethiopia, where 50 million people live in malaria-ridden areas. The government is in the process of employing 30,000 health-extension workers, who, after a full year of training, visit villages and dispense medicines as well as advice for prevention and family planning. They play an indispensable part in delivering ACTs, says Ethiopia’s federal health minister Tedros Ghebreyesus, who also chairs RBM’s board. Ethiopia has also earned praise for delivering almost 20 million insecticide-treated bed nets within the past 2 years.
The program in the northern province of Tigray in which Fanta Dargie participates goes a step further. Instead of distributing ACTs through clinics or salaried health-extension workers, it uses community volunteers who have received just a few days of training. In this trial, supported by WHO and Novartis, researchers are trying to find out whether distributing ACTs this way is safe, what the effects on morbidity and mortality are, and how many are used, says Asefaw Getachew of the Carter Center in Addis Abeba, who coordinated the trial while at the Tigray Regional Health Bureau.

But many are already convinced that distribution through volunteers will prove the way to go—especially for the rural poor who live too far away from a clinic or health post to take their sick child, says Awash Teklehaimanot, a malaria expert at Columbia University’s Earth Institute in New York City who also runs the Center for National Health Development in Addis Abeba. There are concerns about overuse, but the lack of resistance seen so far suggests “that we shouldn’t be too conservative,” he says. “It’s no use hoarding these drugs in health centers when people are dying in the village.”

Private business

But although many applaud Ethiopia for expanding its health-care system, the private market is a different story, and for now, it’s the bigger one. At the moment, some 75% of malaria patients worldwide buy their drugs at a local pharmacy or drugstore, where ACTs, if available at all, are often much more expensive than a bewildering array of older drugs, artemisinin monotherapies, traditional medicines, or counterfeit drugs.

The plan for a global subsidy—although it might also benefit public procurements of ACTs—is hoped to have the biggest impact in this private business. The idea is that consumers will choose ACTs if they cost 10 cents or less; to get there, while still allowing wholesalers and retailers their usual profit margin, a new fund—recently christened Affordable Medicines Facility for malaria (AMFm)—would make a substantial copayment to the producer whenever a wholesale company or government agency decides to buy a shipment of WHO-approved antimalarial drugs. The goal is for the buyer to pay just 5 cents per treatment course—including shipment to the country. The current plan calls for an annual budget climbing to $300 million by 2010; UNITAID has expressed an interest in footing the bill.

First proposed in a 2004 Institute of Medicine report from a group led by economist and Nobel laureate Kenneth Arrow, the idea languished for a while; some worried that a subsidy would line industry’s pockets, whereas existing funding agencies felt it threatened their turf, says Harry van Schooten of the Dutch Ministry of Foreign Affairs, which has been pushing the plan. But it gained traction after a January meeting in Amsterdam, and now agencies such as the Global Fund, UNICEF, and WHO are vying to host the AMFm’s secretariat, he says. RBM’s board is expected to approve the plan at a November meeting.

Still, the devil is in the details, says WHO’s Mendis. Dealers may be tempted to charge high prices for ACTs anyway, for instance. “How do we prevent the subsidy from going to the pockets of the middlemen?” she says. Several measures can help prevent that, answers Van Schooten; ACT packages could have a printed price on them, patients will need to be educated, and countries will have to regulate their domestic ACT market and monitor drug quality. Whether African governments are up to that job remains to be seen.

Other concerns remain as well. A stagnating demand for the raw product in 2007 has caused artemisinin prices to drop from a high of $1100 to $1400 a kilogram to about $200 now. At that rate, farmers can make more by planting rice, says WHO’s Andrea Bosman, who worries about new price hikes and shortages in 2008. And although the lack of resistance to ACTs is encouraging, that is probably just a matter of time, and new drugs need to be developed rapidly, says Ghebreyesus. “What’s plan B? We don’t have alternatives at the moment,” he says.

**Toward eradication?**

But these concerns can’t dampen the sense of optimism in the air for the first time in many years. Whether that means Abuja’s goals can still be met is under dispute. Attaran—who does concede major progress—believes far too much time has been wasted for that. Former Senegal health minister and RBM executive director Awa Marie Coll-Seck asserts they’re still achievable—or at least in some countries. So does Teklehaimanot, who coordinated a Millennium Project working group that proposed setting an even more ambitious goal: a 75% reduction from the 2005 level in 2015.

The truth is that we may never know for sure, says Mendis. Malaria mortality can only be estimated because many patients die at home without being counted, and although much is being done to strengthen data collection, there are few baseline data for 2000 on which claims of success could be based.

But things such as bed-net and ACT coverage can be measured more easily, and where they have shot up, malaria rates appear to be dropping encouragingly fast, she says. In Zanzibar, for instance, where ACTs and bed nets were widely introduced from 2004 on, cases had dropped by almost 90% in the first half of 2006. São Tomé and Príncipe, a small island nation off Africa’s West Coast, has also seen its rates plummeting, says Teklehaimanot. In Ethiopia, malaria now accounts for 10% of deaths, compared with 25% a few years ago, says Ghebreyesus.

Those developments—as well as encouraging reports from vaccine trials—have even brought back a word last heard in the 1960s in the context of malaria: eradication. “To aspire to anything less is just far too timid a goal for the age we’re in,” Melinda Gates, who, with her husband, Bill, has invested billions in the malaria battle, said last week at a meeting in Seattle, Washington.

But others say it’s much too early to talk about that. For White, all the newfound optimism is cause for a new worry: What if the fight is so successful that politicians and donors lose interest? “We better get prepared for the next phase,” he says, “because there will be a lot of good news in the next few years.”

—MARTIN ENSERINK