Current issues in the treatment of uncomplicated malaria in Africa

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Sub-Saharan Africa is faced with a crisis of rising levels of resistance to antimalarial drugs and few available and affordable alternatives. Combination chemotherapy, using two or more drugs with different mechanisms and sites of action together, is proposed as a mechanism for slowing the process of development of resistance. In Thailand, this approach has resulted in a sustained increase in the cure rate. Whether such an effect would be seen in Africa is not known. This article reviews the rationale behind combination therapy, the drugs available and the available evidence from combination therapy trials in Africa. Treatment of uncomplicated malaria in pregnancy and infants is also discussed.

Introduction

The human burden caused by malarial infection is enormous. More than 300–500 million cases of malaria illness are estimated to occur each year, affecting one third of the world’s population. The vast majority of malarial infections cause uncomplicated malaria, with only approximately 1–2% of these episodes becoming severe. Estimates of the annual mortality caused by malaria range from 0.7 to 2.7 million people. More than 90% of these deaths occur in sub-Saharan Africa. Malaria causes absenteeism from work and school, and together with the direct costs of treatment this causes substantial economic and social hardship. For these reasons, the focus of this review will be on the treatment of uncomplicated malaria in sub-Saharan Africa.

The symptoms of uncomplicated malaria are non-specific: fever, chills, rigors, headache and joint pains. By definition it lacks any of the features characteristic of severe malaria, such as repeated fits or vomiting, altered consciousness and severe anaemia. The clinical manifestations depend on the previous exposure of the individual and the degree of immunity acquired as well as other poorly understood parasite factors. Haemoglobinopathies, such as sickle cell trait and thalassaemia, offer some protection from the severe form of the disease. In malaria endemic areas, development of immunity to the more severe forms of the disease comes at a great

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cost; over 75% of deaths occur in children under 5. Chronic infection may lead to anaemia, clinical relapses (recrudescence) and splenomegaly. In high-transmission areas, malaria in pregnancy causes maternal anaemia, prematurity and low birth weight, which is a major risk factor for infantile death. In low-transmission areas and in non-immune individuals, malaria in pregnancy is associated with development of severe disease.

Four species of parasite are responsible for human disease (Table 1). *Plasmodium falciparum* malaria is responsible for nearly all deaths and most of the morbidity. *Plasmodium vivax* accounts for over half of all malaria infections outside Africa and approximately 10% of those in Africa. The definitive diagnosis is made by examination of a blood film, although in high-transmission areas the presence of parasites in the blood does not equate with the patient being ill with malaria. Asymptomatic carriage is the norm in some areas owing to the protective effect of the immune system. In Africa most infections are treated presumptively on the basis of symptoms rather than a positive blood test. This leads to a huge amount of overdiagnosis and consumption of unnecessary and costly drugs. Self-treatment with medicines purchased from a local store or pharmacy, which probably accounts for as much of 50% of drug use in Africa, may lead to the use of inappropriate drugs or underdosing. Initiatives to train local store owners in how to give an adequate dose of antimalarial drugs have been shown to be effective in improving treatment practices. Another serious issue is the widespread use of sub-standard antimalarial drugs in Africa.

The general principles for the treatment of uncomplicated malaria are shown in Table 2. In sub-Saharan Africa, where transmission is generally...
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[Table 2 General principles in the management of uncomplicated malaria]

- The aims of treatment are the prevention of deterioration to severe disease and provision of rapid symptom relief by the cessation of the current infection by killing the blood stage or rings
- In addition to antiparasite treatment, it is important to treat anaemia, maintain hydration and provide antipyretic measures
- Achieving a parasitological cure is not necessarily the goal in high-transmission areas
- A radical cure with the eradication of the hypnozoite stage of *P. ovale* or *P. vivax* is required to prevent future relapse. This may be unrealistic if the patient lives in an area where reinfection is inevitable (in fact the risks of the drug might outweigh its benefits in these circumstances)
- Where possible, use drugs with few adverse effects and simple treatment regimes to promote compliance
- The use of combination therapies should be encouraged wherever possible to prevent or slow the selection of resistance

moderate to high, the main aims of treatment are to prevent the development of severe disease and to produce symptomatic improvement. Since reinfection is almost inevitable, the aim is for a clinical cure and not necessarily to achieve a negative blood slide. ‘Partial immunity’ in non-pregnant adults and older children will normally be sufficient to deal with residual low parasitaemia. In younger children there is concern that patients who remain parasitaemic after treatment may go on to further clinical disease. *Plasmodium falciparum* infection in people living in low-transmission areas and travellers to malarial areas can result in a rapid deterioration due to the lack of effective immunity. Here the aim is to eliminate all parasites from the body and achieve a parasitological cure.

**Drug resistance and combination therapy ‘strategies’**

*Plasmodium falciparum* has developed resistance to most available and affordable drugs. Chloroquine (CQ) resistance was first documented in Southeast Asia in the late 1950s and had spread to Africa by the end of the 1970s. Sulphadoxine–pyrimethamine (SP) has been used as a replacement for CQ but its effectiveness is now also seriously impaired by resistance. Despite this, many countries in Africa still rely on CQ or SP, or combinations of the two, as standard first-line treatment. Quinine is reserved for cases of treatment failure and for severe malaria, but this is a difficult drug to use and is also relatively expensive at about $1 per treatment course. The World Health Organization (WHO) recommends that treatment policy should be changed once clinical failure rates reach 15%. A moment’s reflection would suggest to the clinician that acceptance of up to a 15% failure rate, in a disease that can be fatal, would be unacceptable in most walks of life. Be that as it may, most countries in sub-Saharan Africa have long reached this point and must now decide on their next therapy. The challenge for malaria treatment policy-makers is to find an affordable and effective treatment to which the parasite will not rapidly become resistant.
Resistance is thought to develop by the selection of spontaneous mutations which confer survival advantage in the presence of the drug. Antimalarial drugs with long terminal elimination phases favour this selection process.\textsuperscript{15} In the presence of sub-therapeutic drug concentrations, recrudescence or new infection parasites harbouring a beneficial mutation are preferentially selected. Both CQ and SP have long half-lives, and this has probably contributed to their demise. Resistance to CQ develops with the acquisition of point mutations in the genes $Pfcr$ and $Pfmdr1$.\textsuperscript{13} In the case of SP the key mutations are in the genes $dhfr$ and $dhps$.\textsuperscript{16} A single treatment with SP is associated with the disappearance of fully drug-sensitive parasites and a significant increase in the number of point mutations conferring resistance in both the $dhfr$ and $dhps$ genes in subsequent parasitaemias occurring within 42 days of treatment.\textsuperscript{17}

Combination chemotherapy, using two or more drugs together with different mechanisms and sites of action, is proposed as a mechanism for slowing the process of development of resistance.\textsuperscript{18} This is standard practice in the treatment of HIV and tuberculosis. The probability of mutations arising spontaneously to both drug A and drug B is equal to the probability of a mutation arising to drug A multiplied by the probability of a mutation arising to drug B. Artemisinins have been suggested as ideal drugs for use in combination therapies; this treatment is known as artemisinin combination therapy (ACT). Artemisinins have the broadest antimalarial activity against parasites, from the ring stage to early schizonts, and cause the fastest decline in parasite numbers of all the antimalarial drugs. In a typical adult malaria infection with 2% parasitaemia, the total number of parasites in the individual is approximately $10^{12}$. Every 2 days artemisinins reduce this parasite load by a factor of $10^4$. This compares with factors of $10^3$ for CQ and SP, $10^2$ for mefloquine and 10 for tetracycline.\textsuperscript{19} Where there is a slower kill rate, parasites persist in the blood for longer. Resistant mutations may then be selected in the presence of falling drug concentrations. Artemisinins have very short half-lives and as a monotherapy must be taken for at least 7 days. This is operationally impractical and is likely to lead to high treatment failure rates. As ACT, the artemisinin is taken for 3 days, significantly reducing the parasite numbers and leaving the remaining parasites to be killed by the second drug or the host immune system.

In Thailand, resistance to CQ and SP led to the introduction of mefloquine monotherapy in 1984 as treatment for uncomplicated malaria. Within 10 years treatment failure rates were $>40\%$. The combination of mefloquine with artesunate (ART) was introduced in 1994 and resulted in a sustained high cure rate, a reversal of the \textit{in vitro} mefloquine resistance and a sustained decline in the incidence of $P.falciparum$ malaria in that area.\textsuperscript{20} Whether such an effect would be seen in Africa, where transmission intensity, acquired immunity and treatment practices are very different, is not known and is the subject of much debate.\textsuperscript{21}
Treatment of *P. falciparum* malaria with artemisinins reduces subsequent carriage of gametocytes, the sexual stage of the parasite responsible for infection in the *Anopheles* mosquito. In Thailand this may have been important in reducing the transmission of *P. falciparum* and hence the spread of resistance. In low-transmission areas, because there is little malarial immunity, the majority of people who become parasitaemic are ill and seek treatment. Thus the bulk of parasites and gametocytes are exposed to the effects of the drug. In areas of moderate to high transmission, older children and adults make up the majority of the population who are infectious to mosquitoes. Infections in this group are often asymptomatic and untreated, and so the gametocidal action of the drug may have little impact on overall transmission.

If ACT is to be introduced in Africa, the choice of a companion drug to use in the combination is not clear. An important principle of any combination therapy is that the two drugs mutually protect each other and the parasites should not be exposed to any one drug alone. This is especially important in high-transmission areas where parasite loads are high and people are bitten on a daily basis by infected mosquitoes. In this setting, matching the half-lives of the drugs employed for combination therapy is theoretically beneficial, in that recrudescent parasites or new infections are not exposed to low concentrations of either drug on its own. ART has a short half-life and the options of drugs with which it could be combined are few if this principle is to be followed. Chlorproguanil–dapsone (CD) is one possibility and a combination of this with ART is soon to start Phase III trials.

Combining an artemisinin with a drug with a longer half-life may still prevent or slow the selection of resistance even though the artemisinin will not protect its partner drug during its elimination phase. A 3 day course of ART will reduce the parasite load by a factor of $\sim 10^8$, leaving on average between $10^3$ and $10^4$ parasites for the second drug to clear. The chance of a resistant mutation arising spontaneously is considerably reduced, and the remaining parasites are exposed to the second drug at high concentration. In addition, the reduction in gametocyte carriage should reduce the transmission of resistant parasites. If ART is combined with a drug which is already failing, the patient is in effect receiving artesunate monotherapy but only for 3 days. This may lead to late recrudescence because the primary infection has not been cleared and may also lead to the development of ART resistance.

In high-transmission areas, as well as treating the primary infection, drugs with longer half-lives may have some advantage over short-acting drugs in providing some prophylaxis against new infections. This may be clinically important in terms of numbers of malarial episodes suffered in a year. The down side to this is that this is the very process that drives the selection of resistant parasites. A study in Malawi comparing SP with CD
found that the 14 day clinical cure rate with SP was 80% compared with 95% for CD. Follow-up continued for a year, and children were treated with the same original treatment at each subsequent malarial illness. Despite the higher efficacy of CD, the children in the SP treatment group had no more episodes of uncomplicated malaria, anaemia or severe disease over the year. Similarly, a combination therapy using two non-artemisinin drugs with longer half-lives may have advantages over short acting ACT in some situations in protecting against repeated infections. Unfortunately, resistance levels to CQ, SP, and to a lesser effect AQ are already high and using them in combinations may provide only short lived benefits.

These arguments are of considerable academic interest but, given the crisis now facing sub-Saharan Africa in terms of treatment options, there is little time available for the research to be done to try to answer them. Since 2001, three out of the four combination therapies recommended by the WHO for Africa have contained an artemisinin derivative. The non-ACT is SP–AQ, and this should be ‘mainly limited to countries in West Africa’. The WHO has recently been criticized in the medical literature for continuing to support the use of ‘ineffective’ treatments like CQ and SP, despite this being its policy. Most countries in Africa do not use ACT, mainly because of the cost of implementation of this policy. Changing from SP to SP–CQ or AQ would double the cost of a treatment to roughly $0.20 per treatment. Changing to ACT would increase the cost 10- to 20-fold.

**Combination therapy clinical trials**

There are many published trials comparing different combination therapies for malaria. One difficulty in interpreting these studies is the different efficacy endpoints reported. Traditionally, the goal of treatment in low-transmission areas is to achieve a parasitological cure, i.e. the elimination of all parasites from the body, and the goal in high-transmission areas is a clinical cure. The WHO has recently updated its own endpoints to try to standardize these in a single scheme which includes both clinical and parasitological outcomes. Most studies in Africa report clinical outcome at 14 or 28 days as a primary endpoint. From a public health point of view, documenting the effect of failure to achieve a parasitological cure is important. The continued presence of parasites in the blood after treatment may lead to anaemia, clinical recrudescence and severe disease. Longitudinal studies, where patients are followed over a longer period and given the same treatment at each malarial episode, may allow a better comparison of antimalarial therapies in high-transmission areas.

A meta-analysis of data from 16 randomized trials (12 from Africa) compared the effect of adding 3 days of ART to one of the standard
treatment regimes of CQ, SP, AQ or mefloquine. The study concluded that, for all trials combined, the addition of 3 days of ART to standard antimalarial treatment significantly reduce parasitological failure on days 14 and 28. Gametocyte carriage was also reduced in the ART treated patients. Artemether–lumefantrine (Coartem) is the only fixed-ratio ACT (the two drugs are formulated as a single tablet) registered to internationally recognized standards. Dihydroartemisinin–piperaquine (DHA–PQ; Artekin), another fixed ratio ACT, is in use in parts of Asia. However, DHA–PQ is being prepared for further regulatory scrutiny and this will require additional clinical study, including Phase III trials. Similarly, chlorproguanil–dapsone–artesunate (CDA), which is about to start clinical Phase III trials, is not yet available.

Coartem is being promoted in Africa by the WHO as a first-line treatment for uncomplicated malaria. As a four-dose regime, no benefit was demonstrated in terms of parasitological cure rates when compared with mefloquine, halofantrine and SP. Cure rates were higher only when compared with chloroquine in an area with high chloroquine resistance. A six-dose regime is now recommended, but as yet there is little clinical trial data available to determine whether this will be practical on an operational level or more effective than other options. Non-artemisinin-based combinations of SP plus AQ or CQ proved significantly more efficacious than SP monotherapy in Uganda, and SP–AQ was significantly better than SP–CQ. Gametocyte carriage during follow-up was also significantly less with both combinations.

There are surprisingly few other published studies comparing ACT with non-artemisinin combinations in Africa. A longitudinal study of SP versus SP–ART versus SP–AQ has been performed in Uganda. Patients were treated with the same pre-assigned treatment at each episode of uncomplicated malaria over 1 year, and rates of anaemia, severe malaria and the frequency of malaria episodes were compared. The day 14 clinical failure rate with SP was 18%, which was significantly higher than in the combination therapy groups where failure rates were 1% in each. On extending the follow-up to 28 and 42 days, the SP–AQ group were significantly less likely to have a recrudescence than were those in the other groups. Over the whole year of follow-up, SP–AQ reduced the rate of subsequent treatments for malaria by 54% (P < 0.0001) compared with SP alone, and by 37% (P = 0.007) compared with SP–ART. Haemoglobin rose in all three groups over the follow-up period. This suggests that in this setting, where there was already moderate background resistance, using a combination of two drugs with long half-lives provided some additional protection from reinfections and recrudescence compared with SP–ART. Other studies have shown combinations of ART with more effective drugs like AQ to be very effective.
Brief descriptions of the chief drugs for uncomplicated malaria

The major antimalarial drugs available are listed below with information on cost, side effects and efficacy. This list is not exhaustive and is biased towards treatment options for Africa. More comprehensive reviews are available elsewhere. Most treatment courses for uncomplicated malaria last for 3 days; longer courses are not operationally practical.

Chloroquine (CQ)

CQ is a 4-aminoquinoline with rapid antipyretic and antiparasitic effects. It costs less than $0.10 per adult treatment and is gametocidal. Its main symptomatic adverse effect is pruritus, which is most pronounced in dark-skinned people and may be because of the high affinity of CQ for melanocytes. In the eye this contributes to its retinal toxicity which may be seen after long-term high-dose therapy. Increasing levels of resistance throughout Africa mean that it can no longer be recommended as a first-line treatment for uncomplicated malaria. In some areas, combination with another drug may extend its utility (but this is subject to investigation at present and no conclusions have yet been reached). In Malawi the virtually complete withdrawal of CQ from circulation since 1993 has resulted in the reversal of in vitro CQ resistance and the disappearance of the CQ-resistant genetic phenotype. Whether this effect is reproducible in other African countries would probably depend on how completely CQ could be withdrawn. It does offer the possibility of reintroducing CQ in a combination therapy after a period of absence. CQ remains the treatment of choice for the benign malarias, although CQ-resistant P. vivax has been reported.

Amodiaquine (AQ)

AQ is from the same class as CQ and has the same mechanism of action. It has been shown to have clinical utility even in areas of chloroquine resistance. In the mid-1980s, fatal adverse drug reactions, agranulocytosis and hepatitis were described in travellers taking AQ for prophylaxis. As a treatment it appears safe although we probably have too little data on this point. AQ is inexpensive at $0.15 per adult treatment, and is now being seriously considered for use in combinations with SP or ART. There is concern that if it is used as a treatment with doses taken several times a year, serious adverse reactions may be seen; this concern arises because of the immunogenicity of the drug.
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Sulfadoxine–pyrimethamine (SP)

Although a combination of two drugs, SP is not a combination therapy as the component drugs act on the same target, parasite folate biosynthesis. SP has replaced CQ as a first-line treatment for uncomplicated malaria in many countries in Africa. Unfortunately, resistance has quickly developed, facilitated by its long half-life. SP costs less than $0.10 per adult treatment and is taken as a single dose.

Chlorproguanil–dapsone (CD, Lapdap)

CD is an antifolate combination like SP that is effective against SP-resistant parasites in Africa. In Asia, the parasites carry an additional mutation at position 164 in the gene dhfr which renders CD ineffective. This mutation was detected at very low frequency in Tanzania in 2000 but does not appear to have become more widespread since. The dose is taken over 3 days; both drugs have short half-lives so the selective pressure for resistance is less than for SP. CD was developed by a public–private partnership comprising GlaxoSmithKline, the WHO and the UK Department for International Development. CD is inexpensive and is available in Africa. It can be used as part of an ACT regimen, and the fixed-ratio CD with artesunate (CDA) is under development. As with any new drug, CD (and CDA in due course) will need to be monitored closely now that it is in wider use. Pharmacovigilance will focus on the known adverse event profile of dapsone.

Mefloquine

Mefloquine is a potent drug against P.falciparum resistant to 4-aminoquinolines and antifolate combinations. It is also active against P.ovale, P.vivax and P.malariae. Mefloquine is not a realistic treatment option for uncomplicated malaria in Africa because of its cost (more than $3 per treatment) and frequent symptomatic side effects.

Artemisinins

These include artesunate, dihydroartemisinin and artemether. There is no known in vivo resistance to artemisinins, although there is some worrying evidence of a modest decline in sensitivity in some parts of China. The artemisinins are effective against all human malaria species. ART taken for 3 days in ACT at 4 mg/kg costs a conservative additional $1–2 per treatment. Very few side-effects have been reported,
although animal studies have demonstrated severe neurotoxicity following parenteral administration of high doses of artemether.\textsuperscript{43} These effects have not been demonstrated in humans in any studies to date involving many thousands of patients.\textsuperscript{44} One slight cloud on the horizon may be the recent observation of ototoxicity,\textsuperscript{45} but further work will be needed in this area before the risk can be considered fully documented. The safety of artemisinins in pregnancy is a concern. Teratogenicity has been shown in mammalian models (S.A. Ward \textit{et al.}, unpublished data). However, it is very reassuring that no increased prevalence of birth defects has been noted despite widespread use for many years. The WHO has recommended that artemisinin compounds should not be used for treatment of malaria in the first trimester unless the treatment is considered to be life-saving for the mother; it is unclear how this recommendation will be managed operationally, in areas where pregnancy testing is unavailable. Artemisins should only be used in the second and third trimesters when other treatments are considered unsuitable.\textsuperscript{46} Pharmacovigilance work on the reproductive safety of artemisinins is urgently needed.

\textit{Fixed-ratio ACTs}

\textbf{Artemether–lumefantrine (Coartem)}

Despite a reduced price negotiated by the WHO, Coartem remains expensive ($2.40 per adult treatment) with a dosing regime which may cause adherence problems. It has been adopted as a first-line treatment in several African countries including Uganda and Tanzania.

\textbf{Dihydroartemisinin–piperaquine (DHA–PQ, Artekin)}

Limited clinical studies have shown DHA–PQ to be effective and well tolerated. At a cost of $1–2 for a 2 day treatment course, it may well become an attractive option.\textsuperscript{47} However further pharmacokinetic and efficacy evaluation must be conducted to fulfil rigorous regulatory requirements about its quality, efficacy and safety before its widespread use can be recommended.

\textbf{Chlorproguanil–dapsone–artesunate (CDA)}

Phase II studies are nearly complete and Phase III trials will start in 2005. Like DHA–PQ, CDA is still under development and is likely to become available at about the same time.

\textbf{Pyronaridine–artesunate}

This ACT is under development and is about to start clinical Phase I trials.
Quinine

Quinine is usually reserved as a second-line therapy and for the treatment of severe malaria. Marked side-effects (tinnitus, dizziness, nausea) and a 7 day treatment course mean that it has a limited place as a first-line treatment for uncomplicated malaria.

Halofantrine

Halofantrine is active against all malaria species, but because of its price ($5 per treatment) and serious cardiac side effects it is little used in Africa.

Atovaquone–proguanil (Malarone)

Malarone provides effective treatment against multidrug resistant malaria and as a prophylaxis. It is very expensive ($30 per treatment) and so is likely to be used only in richer countries. It is not a combination therapy; the drugs work synergistically.

Primaquine

Primaquine is used clinically to clear the hypnozoites of *P. ovale* and *P. vivax* and to prevent relapse, and not as a therapy for uncomplicated malaria. *Plasmodium vivax* from Southeast Asia and the Western Pacific region has decreased sensitivity to primaquine, requiring a doubling of the dose or longer duration of therapy to clear the infection. Primaquine may cause acute intravascular haemolysis in patients with G6PD deficiency and is contraindicated in pregnancy and children under 4 years old.

Antibiotics

Antibiotics such as doxycycline, clindamycin and azithromycin have a slow antimalarial activity and have no role as a monotherapy. A 7 day course of doxycycline or clindamycin may be taken with quinine where decreased susceptibility to quinine is suspected. Doxycycline is also used as a prophylaxis.

Treatment of specific groups in sub-Saharan Africa

Adults and children

The treatment chosen will depend on the resources available, the background resistance and the treatment goals of the physician (Table 2). In
addition to antiparasite therapy, patients require supportive treatment to reduce their temperature, maintain hydration and treat anaemia.

**Pregnant women**

In high-transmission areas pregnant women are often asymptomatic (and perhaps aparasitaemic) despite heavy parasite sequestration in the placenta. This can result in maternal anaemia, low birth weight and infant death.\(^7\) Intermittent presumptive therapy (IPT), where SP is given to all women two or three times during pregnancy, is recommended for all pregnant women in high-transmission areas to try to prevent this.\(^48\) The effectiveness of IPT as an intervention is likely to decline with rising resistance to SP, and alternative drugs are required. Symptomatic malaria in pregnancy can be treated with CQ, SP, AQ or quinine. Mefloquine, halofantrine, lumefantrine, CD and atovaquone–proguanil are not recommended in pregnancy at present. As mentioned above, the safety of artemisinins in pregnancy is a concern; however, it should be remembered that the safety of all antimalarial drugs in early pregnancy has probably been inadequately studied.

**Infants**

IPT in infants (IPTi) is being considered as a means of decreasing anaemia and mortality in this high-risk group.\(^49\) In Tanzania, a single dose of SP, given to healthy infants at 2, 3 and 9 months of age at the time of routine Expanded Programme of Immunization (EPI) vaccination, reduced episodes of clinical malaria by 60% and episodes of anaemia by 50% during the first year of life.\(^50\) IPTi is not at present a recommended intervention, and it is not known what effect it would have on drug resistance, the development of malarial immunity or serological responses to the EPI vaccines.

**Conclusions**

Sub-Saharan Africa is facing a crisis due to resistance to the most affordable antimalarial drugs and the need to switch to more expensive regimens. In Africa, where the majority of treatments for malaria are taken presumptively and often unnecessarily, this cost could prove unsustainable. The Global Fund to Fight AIDS, Tuberculosis and Malaria has been set up to provide financial aid to poorer countries to treat these diseases.\(^51\) It is hoped that this will allow poorer countries to implement the best malaria treatment policies and not just those which are the most
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affordable. The benefits of ACT in Southeast Asia are clear to see, but whether the same will be seen in Africa is not certain. More longitudinal studies comparing ACT with non-ACT regimes, where outcomes such as development of anaemia and severe disease can be compared as well as short-term treatment efficacy, are urgently required in Africa to help guide future treatment policies.

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References


