well informed before receiving treatment. The HCTC employs a team of counsellors who are all HIV positive, the majority of whom are on ART.

Starting a patient on ART should be an intensive process, but one that should bring the satisfaction of treatment success.

References available on request.

PREVENTING ANTIMALARIAL RESISTANCE WITH ARTEMISININ-BASED COMBINATION THERAPY

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Malaria morbidity and mortality is rising, principally as a result of increasing antimalarial resistance.[1] Resistance means that there is a shift to the right in the dose-response (concentration-effect) relationship. *Plasmodium falciparum* has developed clinically significant resistance to all classes of antimalarial drugs, with the possible exception of artemisinin derivatives.[2]

Resistance is thought to arise from spontaneous chromosomal point mutations or gene duplications, which are independent of the drug selection pressure. Once formed, these more resistant parasites have a survival advantage in the presence of antimalarial drugs. This is determined by the intrinsic frequency with which these point mutations occur and the degree of resistance conferred by the change.

Several factors encourage the spread of resistance. These include:

- The proportion of transmissible malaria infections exposed to subtherapeutic concentrations of an antimalarial.
- The drug concentration profile (a long elimination phase favours resistance), the pattern of drug use and the level of immunity in the community.

Antimalarial resistance results in prolonged illness, hospitalisation and death as well as a vicious circle of an increase in treatment failure, leading to increased gametocyte carriage and thus increased malaria transmission, particularly of resistant parasites, further increasing drug pressure and antimalarial drug resistance.

In the 1960s resistance to chloroquine developed almost simultaneously in South-East Asia and South America, and has spread remorselessly so that

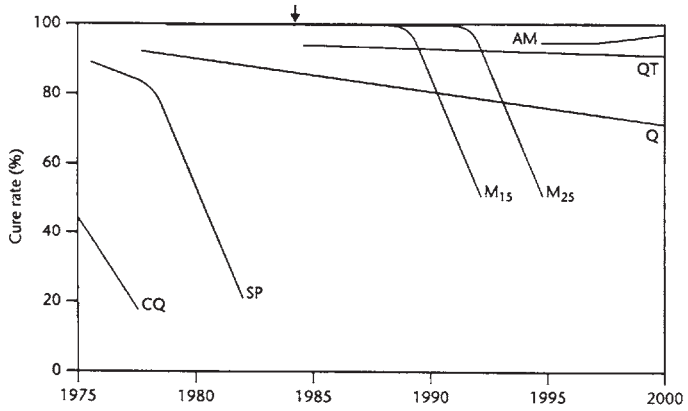

Fig. 1. Antimalarial drug efficacy on the north-western border of Thailand.[7] The decline of antimalarial efficacy of chloroquine (CQ), sulfadoxine-pyrimethamine (SP), mefloquine 15 mg/kg then 25 mg/kg (M15, M25), and quinine (Q) is contrasted with the very slow decline in the efficacy of quinine-tetracycline (QT) and the sustained efficacy of artesunate plus mefloquine (AM).

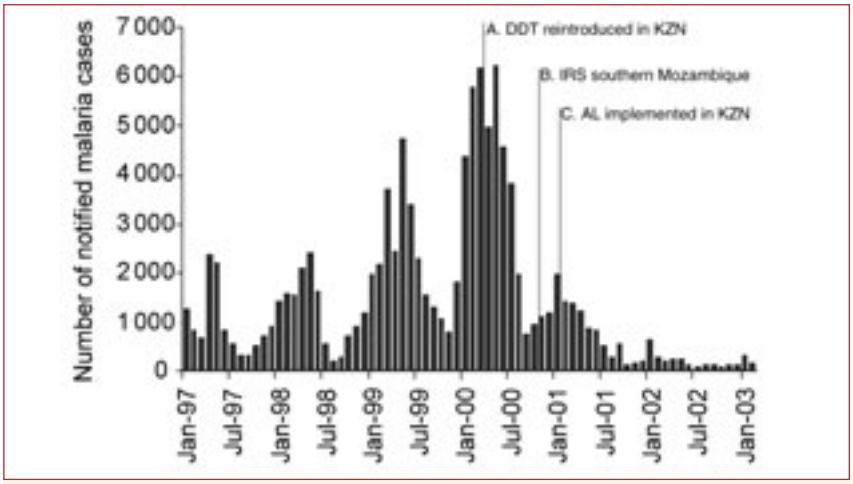

Fig. 2. Number of notified malaria cases in KwaZulu-Natal, South Africa, by month in relation to timing of significant malaria control interventions.

A. Reintroduction of DDT for indoor residual spraying (IRS) of traditional structures in KwaZulu-Natal in March 2000.
B. Introduction of indoor residual spraying (IRS) in southern Mozambique in October 2000.
C. Implementation of artemether-lumefantrine (AL) for the treatment of uncomplicated falciparum malaria in KZN in January 2001.
Source: KwaZulu-Natal Department of Health, South Africa

chloroquine is ineffective in most malaria-endemic areas, including South Africa.[3] Many countries in east and southern Africa then replaced chloroquine with the antifolate, sulfadoxine-pyrimethamine (SP), as first-line treatment for uncomplicated malaria. KwaZulu-Natal introduced SP in 1988, while Mpumalanga and Limpopo changed policy only in 1997. Resistance to SP develops more rapidly than to chloroquine, and by 2000 SP *in vivo* cure rates at 42 days were only 12% in KwaZulu-Natal.[4] This necessitated an urgent change in treatment policy. In contrast, SP cure rates have remained above 90% in Mpumalanga and Limpopo, where SP was introduced 9 years later than in KwaZulu-Natal.[6]

South East Asia (particularly along the Thai-Burmese and Thai-Cambodian borders), has historically developed antimalarial resistance most rapidly, and events there demonstrate the negative consequences of serial monotherapy (Fig. 1). South Africa has a similar intensity and distribution of malaria transmission, and comparable drug regulation to Thailand. In both countries the low intensity of malaria transmission results in few patients developing any protective immunity; consequently almost all infections are symptomatic and result in patients seeking treatment. The reasonable public health care infrastructure results in most malaria infections being treated with an antimalarial, thus increasing drug pressure and the spread of antimalarial resistance.

The emergence of resistance can be prevented by the use of combinations of antimalarials with different mechanisms of action and therefore different targets. For many years the same rationale has been applied in the treatment of tuberculosis, HIV infections and many cancers. Artemisinin derivatives have particular advantages for use in combination therapy, as they result in the most rapid reduction in parasite load. This is significant, as the selection for resistant mutants is dependent on parasite load. Artemisinin derivatives are also the only first-line malaria treatments to act on gametocytes (the stage of the malaria parasite's life cycle responsible for ongoing malaria transmission), thereby potentially reducing malaria transmission and particularly the transmission of resistant strains of malaria. There is growing international consensus that wide-scale systematic implementation of artemisinin-based combination therapy (ACT) is one of few effective measures that will enable malaria-endemic countries to achieve the ambitious goals set in Abuja to 'roll back malaria', particularly the halving of malaria morbidity and mortality by 2010.[8] The introduction of ACT (artesunate plus mefloquine) in north-west Thailand in 1994 has led to a remarkable decrease in malaria transmission and a reversal of the resistance trend, despite the established resistance to mefloquine monotherapy. By 2000 this regimen was still almost 100% effective.[9] A dramatic decline in malaria mortality observed in Vietnam has been associated with the deployment of ACT.[7] Improved cure rates and decreased gametocyte carriage have been confirmed in limited African field trials.[10]

In response to the SP-resistant malaria epidemic in KwaZulu-Natal that peaked in 2000, artemether-lumefantrine was implemented as first-line treatment in January 2001.[5] This, together with concurrent improvements in vector management, resulted in marked decreases in notified malaria cases (Fig. 2) and malaria-related hospital admissions and deaths. In the western border area of Thailand, a 47% reduction in the incidence of *P. falciparum* infections was observed in the 12 months after the introduction of artesunate plus mefloquine.[11] This further improved to a six-fold reduction over a 10-year period.[9] The similar experience of marked public health benefits in western Thailand suggests that the decrease in malaria morbidity in KwaZulu-Natal reflects the benefits of ACT, rather than being specific to artemether-lumefantrine.

Artemether-lumefantrine is administered as a 6-dose (3-day) regimen, and needs to be taken with fat-containing food or drink. Although achievable with adequate patient education, adherence with both these requirements is challenging, as symptom relief often occurs after 3 doses, and those with malaria may not be able to access or tolerate foods containing fat. This provided motivation for the implementation of the simpler and cheaper regimen of artesunate plus SP in the public sector in Mpumalanga (where SP remains effective enough for use in

an ACT), under Section 21 approval of the Medicines Control Council. A marked decrease in malaria case notifications has followed this introduction of ACT (Mpumalanga Department of Health Notification data — not shown).

It should be noted that these beneficial effects on antimalarial resistance and transmission depend on ensuring that the majority of *falciparum* infections are treated with artemisinin-based combinations, and that the use of either component alone is curtailed. This is facilitated by the use of fixed-dose ACT (e.g. artemether–lumefantrine), strict drug regulation and adequate patient education. Patients who receive inadequate treatment (either because of poor adherence, vomiting of oral treatment, underdosing or poor drug quality, etc.) are an especially important source of drug resistance. Delaying the spread of resistance therefore requires correct prescribing of adequate doses of appropriately selected antimalarials and patient education to ensure full adherence to prescribed drug regimens. The widespread use of ACT in the treatment of uncomplicated malaria has played an important role in malaria control in South Africa.

Quinine (preferably in combination with doxycycline or clindamycin), however, remains the preferred treatment in patients with more severe malaria, in pregnant women, and children under 1 year of age with uncomplicated malaria.

Further reading

Department of Health. Guidelines for the treatment of malaria in South Africa, 2002.
www.doh.gov.za/docs/facts-f.html

References available on request.