Dr Christine Manyando and Professor Jean-Pierre Van Geertruyden discuss the developments that have seen cotrimoxazole evolve from an effective antibiotic for HIV-infected individuals into a potential weapon in the fight against malaria in sub-Saharan Africa.

Can you begin by providing a brief history of cotrimoxazole (CTX)?

Consisting of a combination of trimethoprim and sulphamethoxazole, CTX has been used as an antibiotic for half a century. The synergy between its two components was first described in a series of experiments published in the late 1960s that found trimethoprim and sulphamethoxazole to have a greater effect when administered together rather than separately because they inhibit successive steps in the folate synthesis pathway. Since being fully described as having an inhibitory action on bacterial metabolism, the drug has been widely used to treat bacterial infections.

What is the significance of CTX use in HIV-infected individuals?

It is significant because of its effectiveness in combating the opportunistic diseases that are mostly responsible for high death rates among HIV-infected individuals with impaired immunity. Additionally, HIV-infected individuals taking CTX for prophylaxis of opportunistic infections have the added benefit of being protected from malaria. As CTX is seldom used as a prophylaxis in the HIV-uninfected, it’s difficult to judge its efficacy, although we know that CTX is effective in reducing morbidity and mortality in HIV-infected individuals despite high in vitro resistance of common bacterial infections to CTX.

Why are the antimalarial effects of this drug only now be appreciated?

CTX prophylaxis reduces the incidence of clinical malaria in HIV-1 infected individuals. There has been a recent interest in this antimalarial property due to the development of resistance in malaria parasites to sulphadoxine pyrimethamine (SP) – the antimalarial used for intermittent preventive treatment in pregnancy – for which there are currently no available alternatives.

Could you outline the mechanism by which CTX targets Plasmodium falciparum parasites and how this compares to the action of traditional malaria treatments?

CTX has a similar mechanism of action to SP. Just as sulphamethoxazole acts synergistically with trimethoprim, so does sulphadoxine with pyrimethamine – both inhibit successive steps in the folate synthesis pathway. However, partial cross-resistance has been reported so the drugs cannot be taken concomitantly. As an antibiotic, CTX can be administrated daily whereas, during pregnancy, SP can only be used two to three times. Furthermore, CTX has the added benefit of treating any co-morbid bacterial infections that may be present.

What were the aims of the studies that you have carried out into CTX use?

The main aim of the randomised clinical trial we recently conducted was to establish the effectiveness and safety of using daily CTX administration to prevent malaria infection during pregnancy. Additionally, we investigated its consequences for the offspring of both HIV-infected and uninfected pregnant women.

Why is it particularly important to understand the effects of an antimalarial drugs in pregnant women?

It’s important because malaria itself has deleterious effects on the outcome of pregnancy. Therefore, a drug to be used during pregnancy needs not only to be efficacious but also safe enough to treat the disease without adding further concerns to the wellbeing of the mother and the unborn child. Also, if a drug has to be administered as a preventative measure, it’s important to note that the pregnant woman is generally well; thus a drug to be given for this purpose should not cause deleterious side-effects, or else compliance may be a problem and the intended effect not achieved.

Are there safety concerns surrounding the use of CTX to target malaria?

In HIV-infected individuals, the risk of death is perceived to outweigh any safety concerns that may be related to the use of CTX. However, if we suggest that CTX may be an alternative to the increasingly resistant antimalarials used during pregnancy, especially in HIV-uninfected women, prospective studies are warranted to assess efficacy and safety. There is currently a lack of data for the effect on pregnant women, with or without HIV, on the daily use of CTX for malaria prophylaxis because this demographic group is generally excluded from clinical trials due to generic safety concerns.
Since widespread use of the drug cotrimoxazole (CTX) began in the 1970s, its primary function as an antibiotic has overshadowed its antimalarial qualities as an effective treatment for the deadly Plasmodium falciparum parasite. In the last decade in particular, CTX has been increasingly used as a preventative measure against opportunistic infections arising in children and adults infected with HIV. In these individuals, the added benefits of its antimalarial effects have been observed but largely ignored.

Sulphadoxine pyrimethamine (SP) is currently the only antimalarial validated with regards to efficacy and safety for the preventive treatment of pregnant women against malaria. However, increasing resistance of malaria parasites to SP has necessitated the search for alternative drugs and drawn attention to emerging evidence highlighting the antimalarial properties of CTX. This is a particularly promising therapeutic candidate because, over the course of the half century that CTX has been used as an antibiotic in sub-Saharan Africa, there have been no definite signs of resistance developing in malarial parasite populations. Having only recently received widespread attention, the majority of data on CTX concern its use in children and adults infected with HIV. Before it can be considered a safe and effective substitute to SP use during pregnancy, it is vitally important to investigate how this drug affects those without HIV, and pregnant women in particular.

Primary concerns

Currently directing research into the safety and efficacy of CTX and the prevention of malaria during pregnancy is Dr Christine Manyando, Head of the Tropical Diseases Research Centre's (TDRC's) Public Health Department in Ndola, Zambia. Established in 1975 by the World Health Assembly, one of the TDRC's main functions today is to perform clinical and epidemiological research into malaria. Working closely with Manyando is Professor Jean-Pierre Van Geertruyden, Head of the International Health Unit at the University of Antwerp, Belgium.

Reviewing the evidence available on the safety and efficacy of using CTX in antimalarial treatment, Manyando and Van Geertruyden have become well acquainted with the drug's 50 year history. Although there is an absence of data concerning pregnant HIV-negative women, a considerable amount can be gleaned from the studies of HIV-negative and -positive individuals who are not pregnant. All the collated data from studies taking place in sub-Saharan Africa are producing a markedly positive picture. For those with HIV-1, CTX has been shown to reduce incidence of clinical malaria by between 46-97 per cent. For HIV-negative individuals, the researchers have seen incidence reduced by 56-97 per cent.

Though the associated risks of using CTX are considered to be less significant than the boon of treating malaria, concerns regarding increased resistance of other infectious pathogens present a serious impediment to the implementation of a CTX programme. However, a study conducted in Uganda has suggested that antimicrobial resistance among diarrhoeal pathogens does not increase as a result of daily CTX use; in fact, the therapy actually reduced mortality and morbidity in people infected with these infections. Manyando and Van Geertruyden's research shows that 75 per cent of the health concerns associated with CTX use are complaints of nothing more than skin reactions. Investigations to date seem to demonstrate that CTX prophylaxis can be considered both safe and efficacious.

Action in the womb

Despite growing resistance among malarial parasites, SP administration during pregnancy remains a vital preventative measure for parasite-infected pregnant women, as it dramatically reduces malarial episodes, maternal and foetal anaemia; incidences of low birth weight; and placental malaria. Addressing the absence of data on CTX efficacy in pregnant women, Manyando and Van Geertruyden have conducted randomised, open label clinical trials in partnership with Belgium’s Institute of Tropical Medicine to evaluate the effects of daily CTX use to prevent malaria during pregnancy. Assessing a drug's safety is a double concern when unborn children are involved. To examine the developmental effects of CTX prophylaxis on offspring, their weights and gestational ages are recorded at birth along with incidences of perinatal mortality.

Investigations to date seem to demonstrate that cotrimoxazole prophylaxis can be considered both safe and efficacious.
Opting for a region with high rates of malarial infection, Manyando and Van Geertruyden’s study took its sample base from the Kabuta Health Centre, situated in Zambia’s Nchelenge district. With a minimum delivery rate of 10 babies per week, recruiting patients for the trial has proved relatively straightforward despite its sensitive nature. “The local populations are willing to participate in studies as most involve the investigation of priority local health problems,” explains Manyando. With the data from their study still being analysed, the extent of the effects of CTX prophylaxis on HIV-negative pregnant women remains to be seen, but reports made elsewhere hint at the drug’s full potential. In a study conducted in Malawi in 2011, CTX was shown to outperform SP considerably, whether used separately or as an adjunctive treatment for pregnant HIV-positive women. In accordance with a previous report that highlighted CTX treatment as beneficial to birth outcomes, the Malawian study demonstrated increases in haemoglobin concentrations and reductions in the prevalence of maternal anaemia. For HIV-infected women, at least, CTX decreases the risk of placental malaria.

CROSS-RESISTANCE

Concerns over the possibility of a widespread resistance to CTX have understandably arisen due to the common issue of cross-resistance among similarly acting drugs. The likelihood of such a scenario taking place is difficult to ascertain. One report has shown that for both pregnant HIV-positive women on CTX and pregnant HIV-negative women taking traditional SP therapy, a similar prevalence of placental malaria and resistance markers was found. On the other hand, evidence to the contrary is easy to come by, as recent studies in Kenya, Tanzania, Thailand and Uganda did not demonstrate a link between CTX use and increased antifolate resistance in HIV-infected children and adults. Furthermore, CTX treatment appears to have reduced the occurrence of malaria and antifolate resistance genotypes, while the cross-resistance between CTX’s trimethoprim and SP’s pyrimethamine has been shown to be incomplete.

Though CTX’s status has not yet been fully consolidated, these indications come as welcome news for the future of antimalarials. Other alternatives to the increasingly ineffective SP are in development but it will be some time before they are ready for clinical use. If Manyando and Van Geertruyden’s latest study shows CTX prophylaxis to be safe and efficacious in HIV-negative pregnant women, availability should not pose too much of a challenge, as Manyando points out: “This drug is already widely used, relatively cheap and accessible, both as an antibiotic and for prophylaxis in HIV patients”. Before CTX is widely implemented as a viable alternative to SP, replications of Manyando and Van Geertruyden’s clinical trial in other countries experiencing high levels of malaria would ideally be conducted to make a truly sound assessment of its effects. If it is confirmed, the near future could see CTX bridging the gap between SP failure and the next generation of antimalarials.

Malaria and pregnancy

• Throughout Africa, around 30 million women in malaria-endemic areas become pregnant every year
• Up to 200,000 newborn deaths occur each year as a result of malaria in pregnancy
• Malaria is a particular threat to both the mother and the unborn child. Not only are these women particularly susceptible to the disease due to a weakened immune response during pregnancy, but maternal malaria increases the risk of spontaneous abortion, stillbirth, premature delivery and low birth weight.

Dr Christine Manyando and Professor Jean-Pierre Van Geertruyden meet with the chief-tainess in Kabuta, Nchelenge.