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**Cotrimoxazole prophylaxis for HIV-positive TB patients in developing countries**

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**SUMMARY** Despite provisional recommendations from the World Health Organization and UNAIDS that cotrimoxazole (CTX) prophylaxis be offered to all individuals living with AIDS, including HIV-positive patients with TB, its routine use in developing countries particularly Africa has been minimal. Concerns were expressed regarding its effectiveness in areas of high bacterial resistance, that its widespread use might substantially increase bacterial cross-resistance in the community and that this intervention might promote resistance of malaria parasites to sulphadoxine–pyrimethamine.

We review the current evidence on the above concerns and highlight the main operational considerations related to implementing CTX prophylaxis as a basic component of care for HIV-positive TB patients in developing countries.

**Introduction**

Cotrimoxazole (trimethoprim–sulphamethoxazole, CTX) is a widely available, easy to administer, safe and low-cost antibiotic, which is known to have a broad spectrum of action against several HIV-related and non-HIV-related pathogens. In wealthy countries, it has been used widely for primary and secondary prophylaxis to prevent *Pneumocystis jiroveci* pneumonia and *Toxoplasma gondii* encephalitis.1 In high HIV-prevalence countries in the developing world and particularly in sub-Saharan Africa, HIV-positive individuals, particularly those with TB, experience high death rates.2 Unlike the situation in wealthy countries, infections are considered an important cause of mortality, and interventions to prevent such infections might improve survival.3–5

In 1999, a CTX placebo-controlled trial in HIV-positive smear-positive pulmonary TB patients in Cote d’Ivoire showed a 48% reduction in deaths in the CTX group.6 There were significantly fewer admissions due to septicaemia and enteritis in the CTX group than in placebo. CTX was also well tolerated, with only 1% reporting skin reactions. The results of this study were an important factor in persuading the World Health Organization (WHO) and UNAIDS to issue provisional recommendations that CTX be given to all patients in Africa living with AIDS, including HIV-positive patients with TB.7

Despite this blanket recommendation, its routine use in developing countries and particularly sub-Saharan Africa has remained minimal. The main concerns raised at country level were as follows: (a) would CTX be effective in countries that have high rates of bacterial resistance to CTX – the prevalence of bacterial resistance to CTX was low in Cote d’Ivoire; (b) would widespread use of CTX promote community-level rates of antimicrobial resistance; and (c) would CTX increase resistance of malaria parasites to sulphadoxine–pyrimethamine (Fansidar, SP). This drug is still first-line therapy for malaria in several endemic countries.

In this paper, we review the current additional evidence that sheds light on these concerns, and highlight the main operational considerations related to its implementation in HIV-positive TB patients.

**Additional evidence on CTX effectiveness in HIV-positive TB patients?**

A study from South Africa published shortly after the Cote d’Ivoire study produced further evidence showing that adjunctive CTX in HIV-positive TB patients improved survival rates by 53%.3

The recommendations from WHO/UNAIDS made it ethically difficult to justify further placebo-controlled efficacy trials, and Malawi decided to seek evidence on effectiveness by conducting operational research studies on TB patients, using historical controls in two rural
districts of Malawi. In Thyolo district, a package of voluntary counselling and HIV testing (VCT), coupled with CTX for HIV-positive TB patients had an acceptability rate of over 90% and resulted in a 19% reduction in death rate.2 The incidence of side-effects was low with 2% of patients reporting skin rashes. TB patients were also found to be committed to taking CTX, and compliance both during and after anti-TB treatment was over 90%.10,11 In Karonga district, a similar package of VCT and CTX was also well accepted, safe and resulted in a similar 19% reduction in mortality.12 The number needed to treat to prevent one TB death during the 8-month course of anti-TB treatment in both studies was 12.

The scale-up of this intervention under routine programme conditions to other districts has been very encouraging and is associated with improved TB treatment outcomes.13–15

Malawi, like many countries in east and southern Africa, has high rates of in vitro bacterial resistance to CTX in pathogens such as Streptococcus pneumoniae, non-typhoid salmonellae and Escherichia coli.16,17 Nevertheless, the reduction in TB death rates is clear-cut, with a significant benefit in the intervention group.

In South Africa where rates of dual HIV-TB infection were measured at 78%, CTX given to all TB patients irrespective of HIV status showed an overall mortality reduction of 29% when compared with historical controls. The number needed to treat to prevent one death was 24 and the incidence of side-effects was low. The authors concluded that in circumstances where HIV testing for TB patients is not yet operational, it would be feasible, safe and effective to offer CTX to all TB patients as a ‘transitional option’ during anti-TB treatment.18

Unlike the situation in Malawi and South Africa, the Ministry of Health of Zambia decided that despite the evidence from Cote d’Ivoire, placebo-controlled trials should proceed in Zambia, since there was uncertainty about the benefits of CTX in Zambia. A randomized double-blind placebo-controlled trial to evaluate the efficacy of CTX in reducing mortality and morbidity in HIV-positive TB patients showed that despite high levels of drug resistance, CTX was well tolerated, safe and associated with a 16% reduction in hazard ratio of death (Nunn AJ, Wwamba P, Chintu C, Mwinga A, Darbyshire J, Zumla A, unpublished). The effects of CTX were maximal between 6 and 18 months and seemed to wane in the longer term, probably due to falling adherence levels. This study, which is the only one that provides randomized controlled data in TB patients from a high antibiotic resistance setting in Africa adds important evidence to existing non-randomized trials and observational data on the benefit of CTX in TB patients.

Although not conducted in TB patients, a number of additional studies support further the use of CTX in HIV-positive individuals. In a study in Uganda, CTX prophylaxis in HIV-positive individuals was associated with a 46% reduction in mortality, a 72% reduction in the rate of malaria, a 35% reduction in the frequency of diarrhoea and a 31% reduction in the rate of hospital admissions.19 The number needed to save one life per year was 8. These impressive findings occurred, despite the fact that 76% of pathogens isolated from study participants were resistant to CTX. Prophylaxis was also associated with a lower annual rate of decline of CD4 lymphocytes, as well as a lower rate of increase of viral load. The drug (because of its preventive effect on some opportunistic infections) thus seems to have a stabilizing effect on immune deterioration and episodes of viral replication.

Drug compliance was excellent and the incidence of adverse reactions was low at 2%. Although the beneficial effects were most evident in individuals with more advanced HIV-related disease and lower CD4 counts, a subanalysis of the same study found that morbidity and mortality effects were similar across all CD4-cell count strata, and statistically significant reductions in diarrhoea and malaria were observed even among individuals with CD4-cell counts greater than 500 cells/ul. The authors concluded that CTX should be given to all HIV-infected persons, irrespective of CD4 count thresholds.

The only study that has assessed the impact of CTX on community health was conducted in Uganda and showed that CTX taken by those with HIV reduced deaths among HIV-negative family members <10 years old by 63%. Episodes of malaria, diarrhoea and hospitalizations were less among HIV-negative family members.20 This study is the first to show that preventing illness and mortality among those with HIV may improve health and longevity of their family members. The impact might be related to a decreased incidence of diarrhoea and malaria in the HIV-positive individual (taking CTX), which in turn lowers the chance of spread of these pathogens to family members.

Recent additional evidence on the impact of CTX on Plasmodium falciparum malaria infection and disease comes from Mali. CTX prophylaxis in children aged 5–15 years conferred a 99.5% protective efficacy against episodes of clinical malaria, and reduced the prevalence of symptomatic microfoci-confirmed P. falciparum infection by 97%.21

Evidence on CTX efficacy in children is scarce and the only CTX-randomized placebo-controlled trial comes from Zambia. Despite the fact that resistance to CTX in this setting is high (60–80%), the study demonstrated a 43% mortality reduction and a 23% reduction in hospital admissions with the effects seen across all ages and CD4 count strata.22 The benefit was sustained beyond 12 months. This study led to the joint WHO/UNAIDS/UNICEF statement that CTX prophylaxis be a key intervention for all HIV-infected children with symptoms or signs of HIV (by definition, this includes HIV-positive children with TB) and be given to children born to HIV-infected mothers.23

Most of the above studies show that in vitro resistance testing does not reflect the prophylactic ability of CTX, and even in areas with high bacterial resistance, the beneficial effects of this drug are clear-cut.

Does CTX promote antimicrobial resistance in the community?

Although among those taking the drug, CTX prophylaxis increases bacterial resistance to S. pneumoniae and enteric pathogens,17,24 the study by Mermin et al.20 showed reassuring evidence that CTX prophylaxis taken by people with HIV was not associated with increased CTX resistance in stool pathogens isolated from persons living in the same household. This finding does not support one of the main hypothetical objections to the widespread use of CTX among persons with HIV that it might lead to widespread antimicrobial resistance in the community.

Does CTX increase resistance of malaria parasites to SP?

CTX and SP share mechanisms of action and resistance patterns, and concerns about the impact of CTX resistance on SP efficacy have contributed to reluctance.

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to implement CTX prophylaxis in Africa. A randomized controlled study of CTX prophylaxis in children aged 5–15 years from Mali showed that use of CTX did not appear to select for SP-resistant parasites. Considering the clear beneficial effect on morbidity and mortality, the authors conclude that concerns about the spread of SP resistance do not justify further delays in the implementation of CTX prophylaxis. This position is also favoured by the reality that SP will need to be progressively phased out in countries where resistance is already high and replaced by more effective artemisinin-based combination therapies.

**Operational issues**

CTX eligibility criteria for HIV-positive TB patients and specific operational considerations related to implementation are summarized in Boxes 1 and 2, respectively.

In addition to its beneficial effect on morbidity and mortality, there are a number of additional operational advantages in providing this drug to HIV-positive TB patients. First, it provides TB patients with an incentive (an offer) for undergoing HIV testing. As TB often brings the HIV-positive individuals to medical attention, HIV prevalence is relatively high and HIV testing provides an ‘opportunity’ to introduce a range of prevention- and care-related interventions.

Secondly, CTX prophylaxis is a useful intervention for TB patients living in settings yet to have access to antiretroviral therapy (ART) and for those with CD4-cell counts considered too high for ART. In addition, CTX through its stabilizing effect on immune function may delay the time before ART becomes necessary.

Thirdly, CTX prophylaxis could lay the foundation for medication adherence prior to ART and the establishment of HIV-related drug distribution systems within TB programmes. The intervention could also be a first step towards improving the implementation of joint HIV–TB interventions.

Finally, CTX is cost-effective and in addition to preventing illness and deaths among HIV-positive TB patients, the intervention may improve health and longevity of their family members, particularly children. The prevention of orphans is an added benefit.

There are a number of unanswered questions related to CTX that merit priority operational research. In summary, these include the following: determining the
role of CTX in the context of ART, particularly the issue of additive side-effects, and when to discontinue CTX; the need for more observational data on CTX efficacy in Asia and what are the best delivery strategies to improve the uptake of CTX in TB patients. TB and HIV programmes should endeavour to implement CTX prophylaxis as a minimum component of HIV/AIDS care for adults and children in developing countries.

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