infection in a patient receiving highly active antiretroviral therapy. *Clin Infect Dis* 1998;**26**:1008–9
47 Guex AC, Bucher HC, Demartines N, *et al*. Inflammatory bowel perforation during immune restoration after one year of antiretroviral and antituberculous therapy in an HIV-1-infected patient: report of a case. *Dis Colon Rectum* 2002;**45**:977–8
48 Wendel KA, Alwood KS, Gachuhi R, *et al*. Paradoxical worsening of tuberculosis in HIV-infected persons. *Chest* 2001;**120**:193–7
49 Mtei L, Matee M, Herfort O, *et al*. High rates of clinical and subclinical tuberculosis among HIV-infected ambulatory subjects in Tanzania. *Clin Infect Dis* 2005;**40**:1500–7
50 Swaminathan S, Paramasivan CN, Kumar SR, *et al*. Unrecognised tuberculosis in HIV-infected patients: sputum culture is a useful tool. *Int J Tuberc Lung Dis* 2004;**8**:896–8
51 Morris L, Martin DJ, Bredell H, *et al*. Human immunodeficiency virus-1 RNA levels and CD4 lymphocyte counts, during treatment for active tuberculosis, in South African patients. *J Infect Dis* 2003;**187**:1967–71
52 Burman WJ, Jones BE. Treatment of HIV-related tuberculosis in the era of effective antiretroviral therapy. *Am J Resp Crit Care Med* 2001;**164**:7–12
53 Veldkamp AI, Hoetelmans RM, Beijnen JH, *et al*. Ritonavir enables combined therapy with rifampin and saquinavir. *Clin Infect Dis* 1999;**29**:1586
54 la Porte CJ, Colbers EP, Bertz R, *et al*. Pharmacokinetics of adjusted-dose lopinavir–ritonavir combined with rifampin in healthy volunteers. *Antimicrob Agents Chemother* 2004;**48**:1553–60
55 Losso MH, Lourtau LD, Toibaro JJ, *et al*. The use of saquinavir/ritonavir 1000/100 mg twice daily in patients with tuberculosis receiving rifampin. *Antivir Ther* 2004;**9**:1031–3
56 Birgerson L. Vice President, Medical Affairs, Roche. *Important Drug Interaction Warning*. Roche Pharmaceuticals, 2005 [www.aegis.com/files/fda/2005/rifampin_warning_letter.pdf]
57 Zachariah R, Teck R, Ascurra O, *et al*. Can we get more HIV-positive tuberculosis patients on antiretroviral treatment in a rural district of Malawi? *Int J Tuberc Lung Dis* 2005;**9**:238–47
58 STOP TB Parntership. 4 *Million Treatments in 4 Years: Achievement Report 2005*, Geneva: WHO, 2005

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%.[8]

The recommendations from WHO/UNAIDS[7] made it ethically difficult to justify further placebo-controlled efficacy trails, 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.[9] The incidence of side-effects was low with 2% of patients reporting skin reactions. 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 microscopy-confirmed *P. falciparum* infection by 97%.[21]

Evidence on CTX efficacy in children is scarce and the only CTX-randomized placebo-controlled trail 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

Box 1 Cotrimoxazole eligibility in HIV-positive TB patients

Based on WHO clinical staging

- All HIV-positive patients with tuberculosis (pulmonary and extra-pulmonary TB)

Where CD4 testing is available and is being used to guide eligibility†*

- HIV-positive TB patients with CD4 counts <500 cells/uL. This threshold can be considered in areas with high rates of diarrhoeal illness and malaria (e.g. sub-Saharan Africa)
- HIV-positive TB patients with CD4 counts <350 cells/uL. This threshold is advised in settings where bacterial infections are the predominant cause of morbidity
- HIV-positive TB patients with CD4 counts <200 cells/uL. This threshold is sufficient in countries where *Pneumocystis jiroveci* (PCP) and *Toxoplasmma gondii* are the main preventable opportunistic infections (e.g. Asia)

*In children aged less than 6 years, CD4 $<25\%$ irrespective of context. In countries where the adult CD4 threshold level is set at <350 cells/uL or <500 cells/uL, the same threshold level should be applied for children greater than 6 years

†Selection of a specific CD4 threshold should be decided at country level, considering HIV prevalence, burden of opportunistic infection and spectrum of preventable infections and health system capacity

Box 2 Specific operational considerations related to CTX* in HIV-positive TB patients

Drug Regimens

- *Adults*: Dosage is 960 mg per day (800 mg of sulphamethoxazole/160 mg of trimethoprim). This can be given in one dose (as a double strength tablet) or as two single strength (480 mg) tablets taken once or as two divided doses
- *Children*: Dosage is 2.5 mL of syrup for those under 6 months, half an adult tablet (240 mg) daily for those aged 6 months to 5 years old and one tablet (480 mg) daily for those above 5 years to 14 years. Children over 15 years should receive the adult dosage

Contraindications

- Known allergy to CTX or a clear history of severe reactions to sulpha drugs
- First trimester of pregnancy
- Glucose-6-phosphate dehydrogenase deficiency

In case of contraindications, the alternative drug is dapsone, 100 mg daily for adults and 2 mg/kg once daily (maximum 100 mg) for children

Duration of therapy

- CTX should be continued during the entire course of anti-TB treatment and indefinitely thereafter. There is insufficient evidence at present to issue recommendations to discontinue CTX following immune reconstitution on antiretroviral treatment
- CTX should be discontinued in the event of severe cutaneous reaction, renal or hepatic toxicity or severe haematological toxicity

Patient recruitment, drug supply and monitoring

- The entry point to CTX prophylaxis in TB patients is through voluntary counselling and HIV testing
- CTX should be supplied to patients through existing TB drug supply systems. CTX should be provided free of charge
- A specific CTX register would be necessary to monitor follow-ups, side-effects and drug requirements

Training and patient education

- TB staff and counsellors should be made well aware of the importance of CTX prophylaxis
- Patients, care-givers and communities should be made aware that CTX prophylaxis is not a cure for HIV disease, needs to be taken regularly and that it does not replace the need for ART

*Cotrimoxazole

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.[21] 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[25] 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,[26] 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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References

1 Martin JE, Besch CL. Prophylaxis against infections in persons infected with human immunedeficiency virus. *Am J Med Sci* 2004;**328**:64–9
2 Mukadi YD, Maher D, Harries AD. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. *AIDS* 2001;**15**:143–52
3 Gilks CF, Brindle RJ, Otieno LS, *et al*. Life-threatening bacteraemia in HIV-1-seropositive adults admitted to hospital in Nairobi, Kenya. *Lancet* 1990;**336**:545–9
4 Brindle RJ, Nunn PP, Batchelor BIF, *et al*. Infection and morbidity in patients with tuberculosis in Nairobi, Kenya. *AIDS* 1993;**7**:1469–74
5 Greenberg AE, Lucas S, Tossou O, *et al*. Autopsy-proven causes of death in HIV-infected patients treated for tuberculosis in Abidjan, Cote d'Ivoire. *AIDS* 1995;**9**:1251–4
6 Wiktor SZ, Sassan-Morroko M, Grant AD, *et al*. Efficacy of trimethoprim–sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1 infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. *Lancet* 1999;**353**:1469–75
7 UNAIDS. *Provisional WHO/UNAIDS Secretariat Recommendations on the Use of Cotrimoxazole Prophylaxis in Adults and Children Living with HIV/AIDS in Africa*. Geneva, Switzerland: UNAIDS, 2000
8 Badri M, Maarten G, Wood R, Ehrlich R. Cotrimoxazole and HIV-1 infection. *Lancet* 1999;**354**:334–5
9 Zachariah R, Spielmann MP, Chingi C, *et al*. Volunatry counselling, HIV testing and adjunctive cotrimoxazole reduces mortality in tuberculosis patients in Thyolo, Malawi. *AIDS* 2003;**17**:1053–61
10 Zachariah R, Harries AD, Arendt V, *et al*. Compliance to cotrimoxazole for the prevention of opportunistic infections in HIV infected tuberculosis patients in Thyolo, Malawi. *Int J Tuberc Lung Dis* 2001;**5**:843–6
11 Zachariah R, Spielmann MP, Harries AD, Gomani P, Bakali E. Cotrimoxazole prophylaxis in HIV-infected individuals after completing anti-tuberculosis treatment in Thyolo, Malawi. *Int J Tuberc Lung Dis* 2002;**6**:1046–50
12 Mwaungulu FBD, Floyd S, Crampin AC, *et al*. Cotrimoxazole prophylaxis reduces mortality in human immunodeficiency virus-positive tuberculosis patients in Karonga district, Malawi. *Bull World Health Organ* 2004;**82**:354–62
13 Chimzizi R, Gausi F, Bwanali A, *et al*. Voluntary counseling, HIV testing and adjunctive cotrimoxazole are associated with improved TB treatment outcomes under routine conditions in Thyolo district, Malawi. *Int J Tuberc Lung Dis* 2004;**8**:579–85
14 Chimzizi R, Harries AD, Manda E, Khonyongwa A, Salaniponi FM. Counselling, HIV testing and adjunctive cotrimoxazole for TB patients in Malawi: from research to routine implementation. *Int J Tuberc Lung Dis* 2004;**8**:938–44
15 Boeree MJ, Sauvageot D, Banda HT, Harries AD, Zijlstra EE. Efficacy and safety of two dosages of cotrimoxazole as preventive treatment for HIV-infected Malawian adults with new smear-positive tuberculosis. *Trop Med Int Health* 2005;**10**:723–33
16 Walsh AL, Phiri AJ, Graham SM, Molyneux EM, Molyneux ME. Bacteraemia in febrile Malawian children: clinical and microbiological features. *Pediatr Infect Dis* 2000;**19**:312–18
17 Zachariah R, Harries AD, Spielmann MP, *et al*. Changes in *Escherichia coli* resistance to cotrimoxazole in tuberculosis patients and in relation to cotrimoxazole prophylaxis in Thyolo, Malawi. *Trans Roy Soc Trop Med Hyg* 2002;**96**:202–204
18 Grimwade K, Sturm W, Nunn AJ, Mbatha D, Zungu D, Gilks C. F Effectiveness of cotrimoxazole on mortality in adults with tuberculosis in rural South Africa. *AIDS* 2005;**19**:163–8
19 Mermin J, Lule J, Ekwru JP, *et al*. Effect of cotrimoxazole prophylaxis on morbidity, mortality, CD4-cell count, and viral load in HIV infection in rural Uganda. *Lancet* 2004;**364**:1428–34
20 Mermin J, Lule J, Ekwara JP, *et al*. Cotrimoxazole prophylaxis by HIV-infected persons in Uganda reduces morbidity and mortality among HIV-uninfected family members. *AIDS* 2005;**19**:1035–42
21 Thera MA, Sehdev PS, Coulibaly D, *et al*. Impact of trimethoprim–sulfamethoxazole prophylaxis on falciparum malaria infection and disease. *J Infect Dis* 2005;**192**:1823–9
22 Chintu C, Bhat GJ, Walker AS, *et al*. Cotrimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomized placebo-controlled trial. *Lancet* 2004;**364**:1865–71
23 World Health Organization/UNAIDS/UNICEF. *Joint WHO/UNAIDS/UNICEF Statement on Use of Cotrimoxazole as Prophylaxis in HIV Exposed and HIV Infected Children*. WHO/UNAIDS/UNICEF, November 2004
24 Feikin DR, Dowell SF, Nwanyanwu OC, *et al*. Increased carriage of trimethoprim/sulphamethoxazole-resistant streptococcus pneumoniae in Malawian children after treatment for Malaria with sulphadoxine/pyrimethamine. *J Infect Dis* 2000;**181**:1501–5
25 Yazdanpanah Y, Losina E, Anglaret X, *et al*. Clinical impact and cost-effectiveness of co-trimoxazole prophylaxis in patients with HIV/AIDS in Cote d'Ivoire: a trial-based analysis. *AIDS* 2005;**19**:1299–308
26 Danel MR, Sorho S, Sauvageot D, *et al*. Haematological changes in adults receiving a zidovudin-containing HAART regimen in combination with cotrimoxazole in Cote d'Ivoire. *Antivir Ther* 2005;**10**:615–24