

Trimethoprim-sulfamethoxazole decreased morbidity and mortality in HIV-1-infected patients with tuberculosis

Wiktor SZ, Sasan-Morokro M, Grant AD, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Côte d'Ivoire: a randomised controlled trial. *Lancet*. 1999 May 1;353:1469-75.

QUESTION

In HIV-1-infected African patients being treated for tuberculosis, does the addition of trimethoprim-sulfamethoxazole (co-trimoxazole) prophylaxis decrease morbidity and mortality?

DESIGN

Randomized (allocation concealed*), blinded (clinicians and patients),* placebo-controlled trial with median 10.5-month follow-up.

SETTING

4 outpatient tuberculosis treatment centers in Abidjan, Côte d'Ivoire.

PATIENTS

771 patients (mean age 32 y, 60% men) who had sputum smears positive for tuberculosis, were HIV-1-positive or dually reactive for HIV-1 and HIV-2, and met laboratory eligibility criteria (hemoglobin level ≥ 70 g/L, granulocyte count $> 1.1 \times 10^9$ /L, platelet count $> 100 \times 10^9$ /L, serum alanine aminotransferase level < 2.5 times the upper limit of normal, and serum creatinine concentration < 150 g/L). Exclusion criteria were positivity for HIV-2, pregnancy, previously treated tuberculosis, allergy to

co-trimoxazole, or receipt of co-trimoxazole to prevent recurrent toxoplasmosis. 764 patients (99%) were included in the analysis.

INTERVENTION

Patients were allocated to 1 tablet daily of trimethoprim, 160 mg, and sulfamethoxazole, 800 mg ($n = 386$), or placebo ($n = 385$). All patients received tuberculosis medication for 6 months.

MAIN OUTCOME MEASURES

Death and ≥ 1 hospitalization.

MAIN RESULTS

85% of patients in the co-trimoxazole group took $\geq 75\%$ of their medication. During follow-up, fewer patients who received co-trimoxazole died ($P < 0.001$) or were hospitalized ($P = 0.02$) than patients

who received placebo (Table). The rates of death and hospitalization increased with decreasing CD4 cell count. The groups did not differ for adverse events.

CONCLUSION

In HIV-1-infected African patients treated for tuberculosis, the addition of trimethoprim-sulfamethoxazole prophylaxis decreased mortality and need for hospitalization.

Sources of funding: Centers for Disease Control and Prevention; Rockefeller Foundation; Roche African Research Foundation.

For correspondence: Dr. S. Wiktor, Projet RETRO-CI, 01 BP 1712, 01 Abidjan, Côte d'Ivoire. FAX 404-639-4268.

*See Glossary.

Trimethoprim-sulfamethoxazole (co-trimoxazole) vs placebo for HIV-1-infected patients with tuberculosis†

Outcomes at median 10.5 mo	Co-trimoxazole	Placebo	RRR (95% CI)	NNT (CI)
Death	13.3%	22.6%	41% (19 to 57)	11 (7 to 26)
≥ 1 hospitalization	7.6%	12.4%	39% (5.6 to 61)	21 (11 to 172)

†Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

Wiktor and colleagues showed that a simple, inexpensive drug—co-trimoxazole—reduced mortality by 41% in African HIV-1-infected patients with tuberculosis. This study is as important as it is elegant. For the first time, a method to reduce mortality in HIV tuberculosis (which is up to 5 times higher than in HIV without tuberculosis) has been shown. If replicable, these findings could make a vast difference in survival for HIV-1-infected patients with tuberculosis.

The mechanism of such a reduction can only be indirect because co-trimoxazole does not act on *Mycobacterium tuberculosis*. Hovette and Camara (1) from Senegal have shown that nontyphoid salmonella are found as co-infecting organisms in several conditions, including evolving tuberculosis. Greenberg and colleagues (2) from Abidjan have shown that pneumocystosis and bacterial infections also complicate HIV. Lung damage consequent to tuberculosis could increase susceptibility to pneumocystosis and bacterial infections, and the beneficial effect of co-trimoxazole may in fact result from its action in controlling these infections. If these findings are replicated in other developing countries, a landmark in the treatment of

HIV-1-infected patients with tuberculosis will be established, and co-trimoxazole could be routinely included in treatment regimens. In this study, co-trimoxazole prophylaxis reduced the incidence of nontyphoid salmonella sepsis and enteritis caused by isosporiasis and nontyphoid salmonella. Further documentation on the extent and pattern of such co-infections with tuberculosis in patients with or without HIV is urgently needed in developing countries. We must be watchful for the development of resistance when using co-trimoxazole. Whether co-trimoxazole prophylaxis delays the progression of immunosuppression requires further study.

*Manjula Datta, MD, DCH, MSc
Tamil Nadu Dr. M.G.R. Medical University
Chennai, Tamil Nadu, India*

References

1. Hovette P, Camara P. Respiratory manifestations of salmonellosis in AIDS patients. *Int J Tuberc Lung Dis*. 1999;3:743-4.
2. Greenberg AE, Lucas S, Tossou O, et al. Autopsy-proven causes of death in HIV-infected patients treated for tuberculosis in Abidjan, Côte d'Ivoire. *AIDS*. 1995;9:1251-4.