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


**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 \( \geq 70 \) 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 limited of normal, and serum creatinine concentration \( \geq 150 \) 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 \( \geq 1 \) 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 morbidity and need for hospitalization.

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*See Glossary.

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**Commentary**
Wikut 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.

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**References**