**Trimethoprim sulfafoxazole 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 sulfafoxazole (co-trimoxazole) prophylaxis decrease morbidity and mortality?

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

**Setting**
4 outpatient tuberculosis treatment centres 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 (haemoglobin level ≥ 70 g/l, granulocyte count > 1.1 x 10⁹/l, platelet count > 100 x 10⁹/l, serum alanine aminotransferase level < 2.5 times the upper limit of normal, and serum creatinine concentration < 150 µg/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 sulfafoxazole, 800 mg (n = 386), or placebo (n = 385). All patients received tuberculosis medication for 6 months.

**Main outcome measures**
Death and ≥ 1 hospitalisation.

**Main results**
85% of patients in the co-trimoxazole group took ≥ 75% of their medication. During follow up, fewer patients who received co-trimoxazole died (p < 0.001), or were hospitalised (p = 0.02) than patients who received placebo (table). The rates of death and hospitalisation 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 sulfafoxazole prophylaxis decreased mortality and need for hospitalisation.

*See glossary.

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**COMMENTARY**

Witkow 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* from Senegal have shown that non-typhoid salmonella are found as coinfecting organisms in several conditions, including evolving tuberculosis. Greenberg and colleagues* 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 non-typhoid salmonella sepsis and enteritis caused by isosporiasis and non-typhoid salmonella. Further documentation on the extent and pattern of such coinfections 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:**

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**Table:**

<table>
<thead>
<tr>
<th>Outcomes at median 10.5 mo</th>
<th>Co-trimoxazole</th>
<th>Placebo</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>13.3%</td>
<td>22.6%</td>
<td>41% (19 to 57)</td>
<td>11 (7 to 28)</td>
</tr>
<tr>
<td>≥ 1 hospitalisation</td>
<td>7.6%</td>
<td>12.4%</td>
<td>39% (5.6 to 61)</td>
<td>21 (11 to 172)</td>
</tr>
</tbody>
</table>

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