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## Editorials

### Prophylaxis with co-trimoxazole for HIV infected adults in Africa

*Co-trimoxazole reduces mortality even in settings where bacterial resistance may be high*

In their linked study, Nunn and colleagues report the results of a placebo controlled trial of co-trimoxazole prophylaxis in HIV positive Zambian adults being treated for tuberculosis. They found that co-trimoxazole significantly reduced mortality (hazard ratio 0.79, 95% confidence interval 0.63 to 0.99), and they conclude that the findings strengthen the evidence base for the World Health Organization and the Joint United Nations Programme on HIV/AIDS (UNAIDS) guidelines issued in 2000.<sup>1</sup>

We applaud these findings and agree with the conclusion, yet we remain frustrated. The results echo several others published since 1999, but despite the overwhelming body of evidence the findings have been only partially translated into practice.<sup>2 3 4 5 6 7 8 9</sup>

Prophylaxis with co-trimoxazole was used in industrialised countries two decades before it appeared in Africa. In the early 1980s, co-trimoxazole was already being used to prevent bacterial infections in people with granulocytopenia who were HIV negative. In the late 1980s and early 1990s it was shown to prevent first pneumocystosis, then toxoplasmosis, and finally bacterial infections in adults with HIV. Because invasive bacterial infections are rarely life threatening in high income countries, prophylaxis with co-trimoxazole was used mainly to target pneumocystosis and toxoplasmosis, and was recommended for patients with CD4 counts of 200 cells  $\times 10^6/l$  or lower. At this time, research on prophylaxis with co-trimoxazole was just beginning in Africa.

Why were American and European recommendations not transposed directly to Africa? Firstly, evidence indicated that pneumocystosis was rare in African adults. In contrast, HIV related bacterial diseases often caused death.<sup>10</sup> Prophylaxis with co-trimoxazole, which was "primarily antiparasitic" in industrialised countries, therefore needed to become "predominantly antibacterial" in Africa. The implications of this functional shift in policy—especially the question of when to start prophylaxis—was not entirely clear. Secondly, some adults with HIV in industrialised countries were intolerant of co-trimoxazole and had to interrupt treatment. In resource limited settings poor tolerance combined with more limited access to care might alter the risk to benefit ratio of the intervention. Finally, in Africa, HIV is often first diagnosed when patients start treatment for tuberculosis, and tuberculosis is the leading cause of death in patients with HIV.<sup>11</sup> This explains why some studies specifically targeted such patients.

Two placebo controlled trials of co-trimoxazole in Côte d'Ivoire were published in 1999. One was carried out in adults with HIV being treated for tuberculosis, with mortality as the primary outcome. It showed that co-trimoxazole reduced mortality by 46% (hazard ratio 0.54, 95% confidence interval 0.38 to 0.77).<sup>9</sup> The other study was in adults with HIV at WHO stage 2 or 3, with severe morbidity as the primary outcome. It showed that co-trimoxazole reduced severe morbidity by 47% (hazard ratio 0.57, 95% confidence interval 0.43 to 0.75).<sup>2</sup> In both trials, co-trimoxazole was better tolerated than expected. In subgroup analyses both trials

showed that the efficacy of co-trimoxazole was not restricted to patients with fewer than 200 CD4 cells  $\times 10^6/l$ . Co-trimoxazole prevented malaria, invasive bacterial diseases, and isosporiasis. The immediate consequences of this evidence seemed logical. Firstly, two other African placebo controlled trials were stopped prematurely. Secondly, WHO/UNAIDS experts recommended that co-trimoxazole be part of the minimal package of care for African adults with fewer than 500 CD4 cells  $\times 10^6/l$ .

Since 2000, policies on co-trimoxazole have varied widely across the continent, ranging from no prophylaxis to prophylaxis started at different CD4 thresholds. The main argument for deciding not to follow standardised policies stemmed from the question of whether co-trimoxazole will work in countries where bacterial resistance to this drug may be higher than in Côte d'Ivoire. Between 2000 and 2008, six non-randomised studies tackled this question. All found that the answer was "yes."<sup>3 4 5 6 7 8</sup> Further confirmation comes from Nunn and colleagues' randomised trial. Hopefully, their results will convince the very last sceptic.

Invasive bacterial diseases such as tuberculosis are "early" opportunistic diseases. Although their incidence is highest in adults with HIV who have fewer than 200 CD4 cells  $\times 10^6/l$ , these diseases are still more common in HIV infected adults with higher CD4 counts than in those without HIV.

Bacterial diseases such as tuberculosis are curable in settings with high standards of care but cause death when access to diagnosis and treatment is limited.<sup>10 11 12</sup> This is why it is preferable to prevent these diseases. In sub-Saharan Africa, prophylaxis with co-trimoxazole and isoniazid are effective and these drugs should be prescribed. Trials are needed to assess their main alternative—starting antiretroviral therapy earlier.

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