Daily co-trimoxazole prophylaxis reduces mortality in severely immunosuppressed

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Daily administration of a cheap, widely available, antibiotic (co-trimoxazole) as prophylaxis halves mortality in severely immunosuppressed HIV-infected adults starting treatment in Africa; with benefits continuing for at least 72 weeks. Furthermore, co-trimoxazole prophylaxis also reduces malaria incidence. These are the conclusions of an Article published Online First and in an upcoming issue of *The Lancet*.

The study -- an observational analysis of the DART trial published by *The* Lancet in 2009 -- was written by Dr A Sarah Walker, MRC Clinical Trials Unit, London, UK, and colleagues in Uganda, Zimbabwe and the UK.

Co-trimoxazole (trimethoprim-sulfamethoxazole) is a widely available, off-patent, low-cost antibiotic that is used in resource-limited settings to treat and prevent community-acquired infections. In HIV infection, it is highly effective for treatment of and prophylaxis against Pneumocystis jirovecii pneumonia, Toxoplasma gondii, Isospora belli, and bacterial infections; it also has antimalarial properties.

Results of clinical trials and observational studies in HIV-infected adults and children across Africa who are not taking anti-HIV treatment have shown that co-trimoxazole prophylaxis reduces mortality, morbidity, and hospital admissions, even in areas of high background bacterial resistance. WHO guidelines recommend that co-trimoxazole prophylaxis is given to all symptomatic adults with CD4 counts lower than 350 cells

per μL in resource-limited settings, and is continued when people start HIV treatment. However, these recommendations for continuing co-trimoxazole with anti-HIV treatment were based on extrapolation from US studies. There were no African data and concerns about limited benefit and the potential to compromise adherence led to variable use in low-income settings.

Participants in this new analysis were from the DART randomised trial of management strategies in HIV-infected, symptomatic, previously untreated Ugandan and Zimbabwean adults starting triple-drug ART with CD4 counts lower than 200 cells per μL. Co-trimoxazole prophylaxis was not routinely used or randomly allocated, but was variably prescribed by clinicians. The authors estimated the effects of prophylaxis on clinical outcomes, CD4 cell count, and body-mass index (BMI).

The results covered 3179 participants who contributed 14 214 years of follow-up (8128 [57%] person-years on co-trimoxazole). Predictors of co-trimoxazole use were the most recent CD4 cell count, haemoglobin concentration, and BMI; and previous WHO stage 3 or 4 events on ART. Current prophylaxis reduced risk of death by 35% overall. Mortality risk reduction on ART was substantial to 12 weeks (59%), sustained from 12–24 weeks (44%), but not evident after 72 weeks. Variation in mortality reduction was not accounted for by time on co-trimoxazole, nor surprisingly by current CD4 cell count. Prophylaxis also reduced frequency of malaria by 26%, an effect that was maintained with time. Of note, no statistically significant effect of prophylaxis was observed on new WHO stage 4 events (eg opportunistic infections such as oesphageal candidiasis, cryptococcal disease, or extra-pulmonary tuberculosis), CD4 cell count, or BMI.

The authors say: "Since DART participants, who had advanced immunodeficiency and symptomatic disease, had similar characteristics

to those of most patients starting ART in rollout programmes in Africa, our findings should be generalisable."

Furthermore, the authors point out that mortality in patients accessing ART programmes in sub-Saharan Africa is very high in the first year on treatment, with 8% of patients dying, most in the first 3-4 months. Even when baseline immunodeficiency is allowed for, early mortality is several times higher in resource-limited settings than it is in high-income settings.

They conclude: "In DART, adherence was high, and concerns that initiation of both co-trimoxazole and ART together might lead to unacceptably high rates of toxic effects are not substantiated by our data. The mortality benefits, safety, and tolerability, together with the low cost and simplicity of implementation, suggest that co-trimoxazole prophylaxis [combined with anti-HIV treatment] is cost effective and has a substantial public health effect. Our results reinforce WHO guidelines and provide strong motivation for provision of co-trimoxazole prophylaxis for at least 72 weeks to all adults starting combination ART in Africa."

They add: "Whether co-trimoxazole can be stopped after this 72 week period needs further investigation."

In an accompanying Comment, Dr Xavier Anglaret, INSERM, U897, Université Victor Segalen Bordeaux, France, and Dr Serge Eholie, Service des Maladies Infectieuses et Tropicales, CHU de Treichville, Abidjan, Ivory Coast, say: "Why duration of combination ART (cART) is the key determinant of co-trimoxazole efficacy, independent of current CD4 cell count, is uncertain. However, the results of today's study clearly suggest that in sub-Saharan Africa, starting on cART should not be a reason for not starting or for stopping co-trimoxazole, and that prophylaxis should be maintained for more than 1 year after

starting cART. Furthermore, the findings of this study show that important practical questions about HIV management can be answered with cohort data, as long as the study meets standard research criteria. For countries with restricted resources to address such questions, large cohort studies, such as DART, need to be done."

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