Co-trimoxazole in people on antiretroviral therapy for HIV

I read with great interest the meta-analysis of data on the initiation, discontinuation, and dosing of co-trimoxazole prophylaxis in adults with HIV by study of Suthar and colleagues.[1] Their findings reinforce recent WHO recommendations for long-term co-trimoxazole prophylaxis in adults with HIV who are receiving antiretroviral therapy irrespective of CD4 cell count or WHO clinical stage, especially in resource-constrained settings with high prevalences of invasive bacterial diseases and malaria.[2] On the basis of preliminary evidence, continuous co-trimoxazole prophylaxis after antiretroviral-induced immune recovery might provide benefits in resource-rich settings as well.

Patients with HIV are at risk of residual immune dysregulation syndrome even with proper viral suppression.[3] This syndrome is characterised by deregulated immune-coagulation pathways and increased morbidity and mortality caused by non-AIDS events. In this context, the use of co-trimoxazole has been postulated as adjunct therapy, attenuating both T-cell activation and the microbial translocation across impaired gut epithelial barrier common seen in treated HIV individuals. For instance, a substudy of the ARROW trial showed that in patients with HIV on long-term antiretroviral therapy continuous co-trimoxazole prophylaxis was associated with substantially lower concentrations of plasma proinflammatory biomarkers (ie, c-reactive protein, sCD14, interleukin 6) than was interrupted prophylaxis.[4] A randomised, placebo-controlled trial to assess the efficacy of co-trimoxazole in reducing the relapse of Wegener's granulomatosis showed a lower risk of relapses in the interventional arm, emphasising the emergent role of co-trimoxazole as a potent immunomodulatory drug with anti-inflammatory proprieties.[5] Further investigations are urgently required to assess the true effect of co-trimoxazole on the persistent inflammatory state associated with chronic HIV. Whether short-term or long-term prophylaxis will be needed to reduce immune activation in people receiving antiretroviral therapy is unknown; and concerns about drug interactions between and tolerability might arise.

Data from the Swiss HIV Cohort Study have shown that cumulative and current co-trimoxazole prophylaxis reduce all-cause mortality and incident tuberculosis rate in ART-naive and ART-experienced patients.[6] These findings suggest that the protection attributed to co-trimoxazole prophylaxis might be of use in diverse settings including regions with low-burden of infectious diseases in more developed countries.

JAdSM is supported by a scholarship from Programa de Estudantes-Convênio de Pós-graduação (PEC-PG, da CAPES/CNPQ). I declare no competing interests.

José Alfredo de Sousa Moreira
jose.moreira@ini.fiocruz.br

Fundação Oswaldo Cruz (Fiocruz), Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro, Brazil

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2 WHO. 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. http://www.who.int/hiv/pub/guidelines/arv2013/December2014-ARVsupplement-chap8.pdf (accessed March 27, 2015).

3 Lederman MM, Funderburg NT, Sekaly RP, Klatt NR, Hunt PW. Residual immune dysregulation syndrome in treated HIV infection. *Adv Immunol* 2013; **119:** 51–83.

4 Prendergast AJ, bwakura-Dangarembizi M, Musiime V, et al. Lower inflammatory biomarkers in children randomized to prolonged cotrimoxazole prophylaxis. 21st Conference on Retroviruses and Opportunistic Infections; Boston, MA, USA; March 3–6, 2014 (Poster 914).

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6 Hasse B, Walker AS, Fehr J, et al. Co-trimoxazole prophylaxis is associated with reduced risk of incident tuberculosis in participants in the Swiss HIV Cohort Study. *Antimicrob Agents Chemother* 2014; **58:** 2368–68.

Authors' reply

We thank José Alfredo de Sousa Moreira for his interest in our article.[1] Moreira suggested that co-trimoxazole prophylaxis may have benefits beyond prevention of AIDS events in high-income countries, including reductions in non-AIDS events resulting from residual immune dysregulation syndrome and incident tuberculosis. We agree that these plausible benefits require further investigation. If co-trimoxazole is proven effective for these benefits, we welcome research to assess continued use with other key interventions, such as isoniazid preventive therapy and inflammatory reducing drugs in high-income countries.

In a Comment linked to our paper, Badri and Moghraby[2] suggested that the meta-analysis on initiation among adults with CD4 counts less than 350 cells per µL actually had adults with CD4 counts less than 200 cells per µL. Although most participants in this meta-analysis had advanced HIV disease, mortality was significantly reduced in over 2000 person-years with CD4 counts between 200 cells per µL and 350 cells per µL.[3,4] There was also concern that risk differences and hazard ratios were mixed in the same meta-analysis. For the initiation and discontinuation meta-analyses, hazard ratios were used to determine superiority of co-trimoxazole prophylaxis relative to control. Risk differences were used to evaluate the equivalence of different daily doses and the non-inferiority of co-trimoxazole prophylaxis relative to intermittent treatment of malaria in pregnant women. Risk differences and hazard ratios were not mixed in the same meta-analysis.

We hope that the important knowledge gaps identified will be