Eligibility for co-trimoxazole prophylaxis among adult HIV-infected patients in South Africa

To the Editor: Co-trimoxazole (fixed-dose trimethoprim-sulfamethoxazole) is a broad-spectrum antibiotic used to prevent opportunistic infections in patients with HIV infection. Primary prophylaxis with co-trimoxazole has been shown to decrease hospitalisation, morbidity and mortality among people living with HIV, primarily by decreasing rates of malaria, pneumonia, diarrhoea, *Pneumocystis* pneumonia, toxoplasmosis and severe bacterial infections.[1-4] Co-trimoxazole is inexpensive and widely available. In standard adult treatment guidelines and essential medicine lists in South Africa (SA), the current recommendation is that co-trimoxazole should be provided for HIV-infected patients with a CD4+ count <200 cells/μL, HIV/tuberculosis (TB) co-infection and/or advanced HIV disease (World Health Organization (WHO) stage 3 or 4).

Because of expanded access and progression towards initiation of antiretroviral treatment (ART), the WHO issued updated guidelines for co-trimoxazole prophylaxis in 2014.[5] These guidelines recommend co-trimoxazole prophylaxis for adults (including pregnant women) with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with a CD4+ count ≤350 cells/μL. In settings with a high prevalence of malaria and/or severe bacterial infections, prophylaxis is recommended for all patients regardless of WHO clinical stage or CD4+ cell count. However, the timing of discontinuation of co-trimoxazole prophylaxis may vary and is dependent on the malarial/bacterial infection burden in different settings.[5] Therefore, the current WHO guidance should be adapted in the context of a country-specific epidemiological profile and priorities.

The impact and benefit of co-trimoxazole prophylaxis on morbidity and mortality among HIV-infected patients with a CD4+ count ≤350 cells/μL in regions with high infectious disease burdens (irrespective of CD4+ count) have been shown in a good-quality systematic review and meta-analysis that included both randomised controlled trials (RCTs) and observational cohort studies.[6] This extensive systematic review by Suthar *et al.*[6] showed that co-trimoxazole prophylaxis reduced the rate of death when initiated at CD4+ counts ≤350 cells/μL with ART in populations in Africa and Asia. Co-trimoxazole prophylaxis in ART-naive patients with CD4+ counts >350 cells/μL reduced the rate of death and malaria, and continuation of prophylaxis after ART-induced recovery with CD4+ counts >350 cells/μL reduced hospital admission, pneumonia, malaria and diarrhoea in African populations (SA, Zimbabwe, Uganda, Malawi, Mozambique and Ethiopia).[6] While this review largely informed the 2014 WHO guideline update, the findings need to be interpreted in the context of studies included and the varied epidemiological profile across middle- and low-income countries. There were only 2 relatively small RCTs with very few events of key endpoints; therefore, the finding of non-significance was likely (e.g. total of ~5 deaths in both arms from both trials).[7,8] One of the 2 studies was unblinded, and the follow-up in the other study was only 4 months. Ongoing co-trimoxazole prophylaxis was better than discontinuation of the drug at CD4+ counts >200 cells/μL for 3 endpoints with an adequate number of events (pneumonia, diarrhoea and malaria). Furthermore, 8 of 9 studies were conducted in countries with a high burden of malaria and bacterial and parasitic diseases, which is generalisable to the SA context.[9] Although seasonal malaria occurs in the north-eastern parts of SA, the incidence of malaria mortality and morbidity has declined remarkably over time (<10 000 cases annually for the past 10 years).[10] In contrast, in Uganda, >9 million confirmed cases of malaria were reported in the public health sector in 2015.[9] In this review, further stratification of the impact of co-trimoxazole prophylaxis at CD4+ counts <200 cells/μL v. 200 - 350 cells/μL was not available. Lower bacterial resistance to co-trimoxazole is possible among populations included in this review, while resistance to co-trimoxazole in SA is common in patients with community-acquired bacterial infections.[11-13] This potential risk of resistance compounded by the lack of long-term toxicity data needs to be weighed against recommending prophylaxis in populations where benefit has not been established.

Local observational studies suggest no benefit of co-trimoxazole prophylaxis with a CD4+ count >200 cells/μL or in patients who were not WHO clinical stage 3 or 4.[14,15] In an observational cohort of patients attending the adult HIV clinics at the University of Cape Town, SA, the effect of prophylactic low-dose co-trimoxazole on survival and morbidity was examined over a 5-year follow-up period. Co-trimoxazole reduced the hazards of mortality by ~44% and the incidence of severe HIV-related illnesses by ~48% in patients with evidence of advanced immunosuppression (WHO stage 3 or 4) or laboratory measurement of total lymphocyte count <1 250 × 10^6/L or CD4+ count <200 cells/μL. However, no beneficial effect was seen in patients with WHO clinical stage 2 or CD4+ count 200 - 500 cells/μL. A potential limitation of this study was that the sample size of patients with a CD4+ count 200 - 500 cells/μL receiving co-trimoxazole was small and may have been underpowered to observe a significant benefit. In this study, patients on ART were excluded.[14] In another SA cohort study by Hoffmann *et al.*,[15] examining co-trimoxazole effectiveness in reducing mortality risk during ART among persons with a CD4+ count >200 cells/μL and varying WHO clinical stages, overall co-trimoxazole prophylaxis reduced mortality by 36% across all CD4+ count strata. Analysis stratified by baseline CD4+ count showed a similar reduction in mortality risk among persons with a CD4+ count <200 cells/μL, but no statistically significant association was found between co-trimoxazole prophylaxis and survival in the subgroup of persons with a CD4+ count >200 - 350 cells/μL, CD4+ count >350 cells/μL and WHO stage 1 or 2 disease. However, the findings of this study need to be interpreted cautiously for the following reasons: the group with a CD4+ count >350 cells/μL was small (n=917) and might not have had enough events to draw inferences; the study population was a cohort of miners and might not have been potentially representative of the SA population; and, being a non-randomised study, residual confounding might have been a potential limitation.

An earlier Cochrane review established the benefit of initiating prophylaxis at a CD4+ count <200 cells/μL in those with stage 2, 3 or 4 HIV disease (including TB), and discontinuation once the CD4+ count was >200 cells/μL for >6 months.[16] There was a reduction of ~31% in mortality, 27% in morbid events and 55% in hospitalisation. Significant reductions were also detected for bacterial and parasitic infections and for *Pneumocystis jirovecii* pneumonia.

Considering the above-mentioned evidence gaps and lack of generalisability of studies to SA, the current National Essential Medicines List Committee and Adult Hospital-Level Technical Sub-committee do not support the implementation of the updated guidance by the WHO for co-trimoxazole prophylaxis among adult HIV-infected patients. Efforts should be directed towards exploring several research gaps. The impact of co-trimoxazole prophylaxis on morbidity and mortality at higher CD4+ counts in low-malaria-burden areas needs to be investigated further. More data are needed on timing of co-trimoxazole cessation in HIV and TB co-infection in our context.

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