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.2–4 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 progress 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.6–10 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.8 This extensive systematic review by Suthar et al.8 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-naïve 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).8,9 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).8–10 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.8–10 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 2015.11 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 4.14–22 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 x 10⁹/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.,13 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.15 There was a reduction of ~31% in mortality, 27% in morbidity 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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