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Cotrimoxazole as a Potential Effect Modifier of the Association Between Vitamin D Status and Risk of Opportunistic Infection Among HIV-Infected Tanzanian Adults

To the Editor—Sudfeld et al report the risk of developing opportunistic infections (pulmonary tuberculosis, pneumonia, oral thrush, and malaria) among human immunodeficiency virus (HIV)–positive people with low vitamin D levels [1]. They found a statistically significant association between vitamin D deficiency and incident pulmonary tuberculosis, oral thrush, wasting, and >10% weight loss and concluded that a randomized controlled trial was warranted to investigate the benefits of vitamin D supplementation with antiretroviral therapy regimens for people living with HIV/AIDS in sub-Saharan Africa.

After adjustment for baseline age, sex, season, body mass index, disease stage, CD4+ T-cell count, and antiretroviral therapy regimen, no association was found between vitamin D levels and incidence of malaria or pneumonia in the cohort. However, the authors did not investigate cotrimoxazole as an effect modifier of the association between vitamin D status and the risk of opportunistic infection. Indeed, at enrollment, 840 of 1103 study participants had CD4+ T-cell counts of <200 cells/μL and were probably receiving cotrimoxazole, as this is recommended by World Health Organization and Tanzanian Ministry of Health guidelines for the management of HIV infection and AIDS [2, 3]. The fact that more than half of the cohort was receiving opportunistic infection prophylaxis may have caused an underestimate of the true association between vitamin D levels and opportunistic infection outcomes in this study.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Reply to Séraphin

To the Editor—Séraphin raised concerns regarding possible effect modification of the association between vitamin D deficiency and incidence of opportunistic infections and weight loss by receipt of cotrimoxazole prophylaxis in our recently published work [1]. In our study, the majority of participants (76%) had cotrimoxazole prescribed at antiretroviral therapy (ART) initiation because of baseline CD4+ T-cell counts of <200 cells/μL, in accordance with World Health Organization (WHO) guidelines [2]. As a result, we have limited ability to detect effect modification by receipt of cotrimoxazole. In a reanalysis of the data conducted using Cox proportional hazard models with assessment of the statistical significance of interaction with the likelihood ratio test, we found no evidence of effect modification of the association between vitamin D deficiency and pulmonary tuberculosis (P = .82 for interaction), oral thrush (P = .98), pneumonia (P = .38), malaria (P = .78), wasting (P = .63), or >10% weight loss (P = .26) by receipt of cotrimoxazole. Separating any effect modification by cotrimoxazole prophylaxis and CD4+ T-cell count will be difficult, since low CD4+ T-cell count is an indication for cotrimoxazole prophylaxis in many resource-limited settings. Although we cannot rule out effect modification by cotrimoxazole, the biological mechanism that would lead to an antagonistic relationship between vitamin D and the study outcomes is not clear.

Séraphin suggested that we underestimated the true association of vitamin D with outcomes; however, we argue that this is a matter of the generalizability rather than the internal validity of our study. Because of the composition of our study population, we are unable to detect modest effect modification by receipt of...