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
cotrimoxazole or high CD4+ T-cell count at ART initiation; however, this does not detract from the validity and generalizability of our findings to similar populations of adults initiating ART at low CD4+ T-cell counts in resource-limited settings where cotrimoxazole is provided according to WHO guidelines. Accordingly, our study results indicate a possible beneficial effect of vitamin D supplementation as an adjunct treatment to ART in much of sub-Saharan Africa, as well as other resource-limited settings. Nevertheless, we strongly support conduct of additional observational studies and randomized controlled trials of vitamin D supplementation to determine whether this relationship is causal.

Notes

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References
