To the Editor—We thank Leung and Yew [1] for their insights into our study [2]. Although some benefit of micronutrient supplementation was observed among HIV-uninfected patients, it is noteworthy that a protective effect on a key primary end point of the trial—namely, short-term recurrences of tuberculosis (TB)—was stronger in the HIV-positive cohort.

We acknowledge that there could be some misclassification of early TB recurrences because of false-negative culture results at 1 month. This misclassification would be of potential concern if it were different by treatment arm. We would not expect differential misclassification given the randomized and blinded nature of our trial. Of note, among HIV-positive participants, the number with negative culture results at 1 month was somewhat larger in the micronutrients arm (n = 130) than in the placebo arm (n = 111). It could be argued that false recurrences after 1 month could have been more frequent in the micronutrients arm because of a larger number of false-negative culture results at 1 month; this could have spuriously inflated the treatment effect. To address this issue, we conducted supplemental analyses testing the effect of micronutrients on recurrences after 1 month after the initiation of treatment, regardless of the culture result at 1 month. Using this approach, the cumulative incidences of TB recurrence between 1 and 8 months were 23 of 193 and 12 of 201 in the placebo and micronutrients arms, respectively (relative risk, 0.50 [95% confidence interval, 0.26–0.98]). This indicates that culture misclassification at 1 month is unlikely to have affected the treatment effect we reported.

Our trial was not powered to specifically examine the effect of treating specific underlying nutritional deficiencies among patients with TB or to assess interactions between an overall indicator of nutritional status (such as body mass index) and treatment assignment on the outcomes studied. It would be informative to elucidate whether addressing specific nutritional deficiencies results in improved outcomes of infectious challenges. However, whether such an approach would yield benefits at the time of translating the findings of clinical trials into clinical practice is open to debate. In resource-limited settings, where TB and other infectious diseases are highly prevalent, multiple nutritional deficiencies usually coexist. In addition, the resources needed to assess specific nutritional deficiencies are seldom available at the patient level.

We agree that addressing the effect of nutritional interventions as adjunctive therapy to other antimicrobial treatments is an important future research endeavor.

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References

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Ethical Consideration for Use of Carbapenems as Treatment for Sepsis Due to Carbapenem-Resistant Bacteria

To the Editor—A generally held medical principle is the avoidance of the use of an antibiotic for the treatment of an infection in which the pathogen has demonstrated in vitro resistance to the antibiotic, especially when alternative agents are available that could be expected to produce a better clinical outcome. Zhang et al. [1] recently published a study in which 2 experimental agents plus a carbapenem were compared with a carbapenem plus placebo for the treatment of sepsis due to organisms known to be resistant to carbapenem. Although the pub-