The problem with vitamin D supplementation for tuberculosis

“We were hungry all the time”, is the first thing a 28-year-old tuberculosis survivor from rural Haiti told one of us (JF) when asked in 2017 about his experience of being treated for the disease. This patient had been cutting sugar cane to support his family of seven—all of whom lived in a one-room shack—but had to stop his gruelling labour once he became sick with tuberculosis, both because of his physical symptoms and because he had to go to the clinic daily for directly observed therapy. Without his income, his family fell into ruin and the pressing need to feed his children became his most urgent priority. “It was hard to take my treatment when the little ones were holding their bellies and crying. We lost so much to TB.”

Tuberculosis is a disease that is more commonly found in individuals living in poverty, and it is also a cause of extreme socioeconomic stress.1 This well documented issue is one of the reasons that the first goal of WHO’s End TB Strategy is to eliminate catastrophic costs by the end of 2020 for people living with tuberculosis.2 The global tuberculosis community is very likely to fail in reaching this goal because most countries are still carrying out baseline surveys on the socioeconomic consequences of tuberculosis. However, food insecurity has been documented for decades as a serious problem for people living with tuberculosis and their households, and can help predict who will develop tuberculosis among exposed household contacts.3 Furthermore, malnutrition is a predictor of tuberculosis outcomes.4 Although food is generally not provided to most people with tuberculosis—except through some commendable projects—there is an abundance of research looking at vitamin deficiencies in this population, with a focus on vitamin D.5 Even when patients with tuberculosis were being sent to sanitoria, the so-called sunshine cure was touted as an important source of vitamin D, and, theoretically, there are multiple reasons why supplementing this vitamin could potentially benefit patients with tuberculosis. Observational studies suggest that low vitamin D concentrations might be associated with an increased risk of tuberculosis and with increased mortality from the disease,6 but there has yet to be convincing data from a rigorous interventional trial to support vitamin D supplementation for people to prevent tuberculosis and its complications.

The study by Christopher Sudfeld and colleagues7 in The Lancet HIV is a well designed, randomised, placebo-controlled study assessing the effect of vitamin D3 supplementation in people with low serum 25-hydroxyvitamin D concentrations. The study was done at four sites in Dar es Salaam, Tanzania among people who were newly diagnosed with HIV. The intervention group received weekly vitamin D3 supplementation at a dose of 50000 IU along with antiretroviral therapy (ART); the control group received a placebo and ART. The primary outcomes of interest were death (in the intention-to-treat population) or incident pulmonary tuberculosis (in a modified intention-to-treat population) over a 12-month follow-up.

Sudfeld and colleagues7 found that although the vitamin D3 was well tolerated, there was no effect of vitamin D3 supplementation on the risk of mortality (hazard ratio 1·04, 95% CI 0·85–1·25; p=0·73) or on incident pulmonary tuberculosis (0·78, 0·54–1·13; p=0·19). The authors note in the subgroup analysis that there might have been some mortality benefit to vitamin D3 supplementation among people with stage IV HIV disease who developed pulmonary tuberculosis, and that there might have been some reduction in the incidence of sputum-smear positive tuberculosis among patients who received vitamin D3 compared with those who received placebo. Sudfeld and colleagues7 conclude by stating that their findings need to be assessed in future trials. Of note, there were no socioeconomic status, food insecurity, or catastrophic costs measures reported in the study, and although study participants received nutritional counselling, there was no provision of food support to participants. Tanzania is a country where more than one in four people are living in poverty and where substantial financial effects associated with tuberculosis have been well documented.8 These issues are further reflected in the baseline characteristics of the participants in Sudfeld and colleagues’ study: more than one in five people enrolled were underweight, with a body-mass index less than 18·5 kg/m² (22% in the intervention group; 20% in the placebo group). Of the 6250 people with HIV who were screened for enrolment, 4848 (77·7%) were found to have serum vitamin D deficiency. Although the causes of vitamin D deficiency are multifactorial, a diet
devoid of micronutrients is an important contributor in poverty-stricken households.9

Are more clinical trials on vitamin supplementation in people living with tuberculosis really a priority as suggested by Sudfeld and colleagues? Even the most basic of these studies cost millions of dollars to implement. Why is providing such research funding in the tuberculosis field considered a priority but providing hungry patients with vitamin supplementation in the form of food is not? There is a notable proverb in Haiti—which is quoted in the book Mountains Beyond Mountains—that “providing sick people medicine, but no food, is like washing one’s hands and drying them off in the dirt.”10 The tuberculosis community needs to stop focusing on vitamin tablets to prevent this disease and its associated complications, and collectively begin to address the dire socioeconomic needs of people who are living with tuberculosis.

We declare no competing interests.

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Chasing the cabotegravir tail: implications for prevention

HPTN077 was a phase 2 trial of long-acting cabotegravir for pre-exposure prophylaxis (PrEP) for HIV infection.1

In The Lancet HIV, Raphael Landovitz and colleagues2 describe the safety and pharmacokinetic tail (ie, how long the drug persists after final administration) of cabotegravir. The authors estimated that injectable cabotegravir might remain detectable after discontinuation for nearly 3 years in men and 4 years in women. Higher body-mass index (BMI), irrespective of sex, also contributed to longer exposure. Despite this, less than 10% of the variability in the tail was explained by sex and BMI, highlighting that there is more to learn about the pharmacokinetics of long-acting cabotegravir.2

These results corroborate that the pharmacokinetic tail must be considered during the implementation of long-acting injections for PrEP. The prolonged exposure of cabotegravir is aptly described by Landovitz and colleagues as “simultaneously an advantage and a limitation”. The pharmacokinetic tail of cabotegravir offers the advantage of ongoing protection despite delayed doses. However, the pharmacokinetic tail also presents a period of risk for selection for viral resistance in the setting of incident HIV infection. Emergent integrase resistance mutations were observed in one macaque study of cabotegravir for PrEP,3 and whether the tail is an actual or theoretical risk will be informed by phase 3 trials and post-marketing experience.

These results demonstrate the importance of investigating sex differences in drug exposure and drug response a priori. I congratulate Landovitz and colleagues for enrolling 66% female participants in HPTN077 and for doing these safety and pharmacokinetic analyses. The assumption that sex does not influence the pharmacological properties of some medications is no longer valid. In macaque studies, female animals required higher cabotegravir concentrations than did male animals for protection against simian HIV infection.2 Similarly, women must maintain near perfect

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8 Madan J, Linnroth K, Lackri S, Squire SB. What can disssaving tell us about catastrophic costs? Linear and logistic regression analysis of the relationship between patient costs and financial coping strategies adopted by tuberculosis patients in Bangladesh, Tanzania and Bangalore, India. BMC Health Serv Res 2015; 15: 476.