



### Vitamin D deficiency increases risk of TB among people starting HIV therapy

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Vitamin D deficiency is associated with an increased risk of pulmonary tuberculosis (TB), oral thrush and wasting among people starting HIV therapy in Tanzania, investigators report in the online edition of the *Journal of Infectious Diseases*. People with vitamin D deficiency were almost three times more likely to develop TB than those with adequate levels of the vitamin.

‘Vitamin D supplementation may be a low-cost adjunct to ART (antiretroviral therapy) if found to be safe and effective in reducing morbidity and mortality,’ comment the authors.

Access to ART is increasing in resource-limited settings, including sub-Saharan Africa. However, patients in this region often start HIV treatment when they have a very low CD4 cell count and are therefore at high risk of developing serious infections during the early months of ART, a period of immune recovery. Treatments that hasten immune reconstitution are therefore needed.

Vitamin D may be such a therapy and is known to have a potent effect on the immune system.

Investigators from the Trial of Vitamin and HAART in HIV Disease Progression had already shown the benefits of oral supplements with vitamins B, C and E for people starting ART. They now wished to see if vitamin D levels were associated with HIV disease progression.

They designed a prospective study involving 1 103 people who were starting HIV therapy. Vitamin D levels were assessed at baseline and then at monthly follow-up appointments. Vitamin D deficiency was defined as a level below 20 ng/ml; vitamin D insufficiency was a level between 20 and 30 ng/dl.

The authors explored the relationship between vitamin D and the risk of diagnosis with TB, oral thrush, wasting, weight loss of 10%, pneumonia, anaemia and several symptoms. A total of 1 103 participants were enrolled in the study and follow-up lasted for a median of 21 months.

Most (79%) of the participants were women, and 80% had a CD4 cell count below 200 cells/mm<sup>3</sup> when they started HIV therapy. Baseline vitamin D deficiency was diagnosed in 9% of participants, with a further 43% categorised as having vitamin D insufficiency.

Pulmonary TB was diagnosed in 4% of participants during follow-up. After taking into account potentially confounding factors, vitamin D deficiency was associated with an almost three-fold increase in the risk of pulmonary TB (HR=2.89; 95% CI 1.31 - 7.41;  $p=0.027$ ). The relationship between vitamin D deficiency and an increased risk of TB persisted when the investigators excluded from analysis those diagnosed with the infection within two months of starting HIV therapy (HR=3.77; 95% CI 1.43 - 9.97;  $p=0.008$ ). This suggested a direct relationship between vitamin D deficiency and the development of TB.

‘There are multiple direct immune mechanisms through which vitamin D deficiency may impair antimycobacterial immunity and increase the risk of tuberculosis reactivation or active primary infection,’ write the authors. ‘Vitamin D may also indirectly reduce the incidence of pulmonary tuberculosis by slowing HIV disease progression.’

During follow-up, some 102 participants were diagnosed with oral thrush. The risk of oral thrush was almost two times greater for those with vitamin D deficiency (HR=1.96; 95% CI 1.01 - 3.81;  $p=0.046$ ) compared with participants with adequate amounts of the vitamin.

Wasting (body mass index (BMI) below 18.5) was diagnosed in 60 participants, and this outcome also had a significant association with vitamin D deficiency (HR=3.1; 95% CI 1.33 - 7.24;  $p=0.009$ ). The association between an increased risk of wasting and vitamin D deficiency remained significant after excluding people with pulmonary TB (HR=2.94; 95% CI 1.19 - 7.23;  $p=0.019$ ). Loss of 10% or more of body weight was also associated with vitamin D deficiency (HR=2.1; 95% CI 1.13 - 3.91;  $p=0.019$ ).

‘These are important findings in light of strong negative associations between mortality and weight loss after ART initiation,’ write the investigators. ‘Vitamin D may influence the incidence of wasting or weight loss directly, through immunomodulatory effects, or indirectly, by reducing incidence or severity of comorbid infections that contribute to weight loss.’

There was no relationship between vitamin D insufficiency and disease progression. Nor did the investigators find an association between vitamin D levels and the risk of anaemia, pneumonia, malaria, or symptoms such as diarrhoea and neuropathy.

The author of an editorial accompanying the study believes the findings ‘add to the evidence suggesting that vitamin D deficiency is an important risk factor for the development of tuberculosis. Clinical trials are required to resolve this issue, and the results presented here provide a rationale to include ART-treated HIV-infected patients in these studies.’ Should the results prove that vitamin D supplements are effective at preventing TB in people with HIV, ‘this nontoxic and potentially highly cost effective intervention could have a significant impact on public health in many of the countries most affected by the HIV pandemic.’

Sudfield CR, et al. Vitamin D status and incidence of pulmonary tuberculosis, opportunistic infections, and wasting among HIV-infected Tanzanian adults initiating antiretroviral therapy. *J Infect Dis*, online edition, 2012. [<http://dx.doi.org/10.1093/infdis/jis693>]

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