The Effect of Antiretrovirals on Vitamin D

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(See the article by Dao et al, on pages 396–405.)

There has been growing interest in vitamin D status and metabolism in patients with human immunodeficiency virus (HIV). Osteoporosis and fractures, as well as many of the extraskeletal conditions associated with vitamin D deficiency, including diabetes, dyslipidemias, and cardiovascular disease [1], are increasingly recognized in HIV-infected individuals. The relationships of these complications to vitamin D status among HIV-infected patients, as well as the effects of antiretroviral therapy (ART) on vitamin D metabolism, are important areas of research. In addition, as a result of the known effects of vitamin D on innate and adaptive immunity [2–4], there is growing interest in determining whether vitamin D deficiency increases the risk of inadequate immune reconstitution, opportunistic infections, and AIDS-related mortality. Recent data from a cohort of pregnant HIV-infected women in Tanzania who were given multivitamin supplementation (not including vitamin D) revealed that vitamin D insufficiency/deficiency at baseline was associated with increased risks of HIV disease progression, anemia, and all-cause mortality, as well as mother-to-child transmission of HIV [5, 6].

Vitamin D, in the form of cholecalciferol, or vitamin D_3, is synthesized in the epidermis when UV-B exposure is adequate. Additional vitamin D can be obtained from diet and supplements, in the form of ergocalciferol (D_2) from plant sources or cholecalciferol from animal sources. Vitamin D from cutaneous manufacture or dietary intake is converted by one of several high-capacity cytochrome P450s to 25-hydroxy vitamin D (25OHD). This form of vitamin D is the most stable and abundant metabolite and is therefore the best indicator of an individual's vitamin D status [7]. Conversion of 25OHD to the active form of vitamin D, $1,25(OH)_2D$, is catalyzed by the mitochondrial enzyme CYP27B1-hydroxylase. This enzyme is principally located in the proximal tubular epithelial cells of the kidney, where its activity is stimulated by parathyroid hormone and inhibited by fibroblast growth factor-23. In addition, $1,25(OH)_2D$ induces the expression of the enzyme 25-hydroxyvitamin D-24-hydroxylase (CYP24), which catabolizes both 25OHD and $1,25(OH)_2D$ into inactive calcitroic acid [1]. Many extrarenal tissues, including monocytes/macrophages, also contain the enzyme CYP27B1, as well as the vitamin D receptor. The vitamin D receptor is a member of the superfamily of nuclear hormone receptors. It functions as a heterodimer with the retinoid X receptor for regulation of vitamin D target genes [8]. In these extrarenal tissues, $1,25(OH)_2D$ acts as a local cytokine. In monocytes, interaction of $1,25(OH)_2D$ with the vitamin D receptor modulates the innate immune response to invading microbes [7]. This process has been shown to be dependent on the availability of adequate serum concentrations of 25OHD and increases in response to vitamin D supplementation [9]

In this issue of the journal, Dao et al [10] use baseline data from the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN), involving a prospective observational cohort of HIV-positive adults from the United States, to estimate the prevalence of vitamin D insufficiency/deficiency, defined as serum 25OHD levels of <30 ng/mL, in comparison with data from the National Health and Nutrition Examination Surveys (NHANES) database. Multivariate models involving HIV-infected participants were used to determine risk factors for vitamin D insufficiency/deficiency.

The age-, race-, and sex-adjusted prevalence of vitamin D insufficiency/deficiency was high among HIV-infected individuals (70%) but lower than that among US adults (79%) from the NHANES database. Among HIV-infected individuals, factors associated with vitamin D insufficiency/deficiency in multivariate analysis were non-Caucasian race, higher body mass index, hypertension, lack of exercise, decreased UV exposure,

Received 29 October 2010; accepted 18 November 2010.
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Clinical Infectious Diseases 2011;52(3):406–408

1058-4838/2011/523-0001$37.00
DOI: 10.1093/cid/ciq169

and a glomerular filtration rate (GFR) of >90 mL/min. Analysis of ART effects on vitamin D status revealed that use of efavirenz was associated with greater odds of vitamin D insufficiency/deficiency in multivariate regression models. The duration of efavirenz use was also independently associated with 25OHD levels. Use of ritonavir or tenofovir was associated with higher levels of 25OHD in some models, but these relationships were not consistent.

An important strength of this study is its size; to our knowledge, this is the largest published cohort study to examine 25OHD levels in HIV-infected individuals that includes a reference group, which helps to place the results in a broader context. Other cohort studies with prospectively recruited HIV-infected and uninfected participants from the United States reported prevalences of vitamin D insufficiency/deficiency among HIV-infected participants but found no difference in prevalence according to HIV status [11–13]. The majority of risk factors identified, including non-Caucasian race, increased body mass index, and decreased UV exposure, have been reported in other cohorts of HIV-infected and uninfected individuals [11, 14–16]. In a finding unique to this study, renal insufficiency, defined as a GFR of <90 mL/min, was associated with higher levels of 25OHD. This finding is contrary to many reports that in chronic kidney disease both 25OHD and $1,25(OH)_2D$ levels are decreased [17–21]. Analysis using 25OHD and GFR as continuous variables or use of a lower threshold for renal insufficiency, particularly because $1,25(OH)_2D$ levels do not significantly decline until GFR is well below 60 mL/min [19], might have led to the detection of other associations between renal function and 25OHD. Information regarding dietary intake of vitamin D, individual assessment of UVB exposure, and parathyroid hormone levels would also be helpful to assess modifiable risk factors and clinical relevance.

The most important contribution of this study is its exploration of the effect of specific ARTs on 25OHD levels. The data for efavirenz are especially compelling, since associations remain significant after adjustment for covariates and in a model containing duration of ART. The association between efavirenz use and decreased 25OHD levels has been reported in other large cross-sectional studies [22, 23], and its effects may differ by race [16]. More compelling data come from longitudinal studies that demonstrate a 5 ng/mL decrease in 25OHD within 6–12 months after initiation of an efavirenz-based regimen [24] and an increase of 25OHD in participants who switch from an efavirenz-based regimen to a darunavir-based regimen [25]. Unfortunately, Dao et al [10] do not provide 25OHD levels stratified by treatment group for comparison.

The effect of efavirenz on vitamin D metabolism is hypothesized to occur through the induction of 24-hydroxylase, a cytochrome P450 enzyme, that inactivates 25OHD and 1,25OHD, similar to the effects of antiepileptics [24, 26, 27]. However, the exact mechanism and whether 24-hydroxylase activity is attenuated over time have not been established. Furthermore, the clinical importance of a 5 ng/mL decrease in 25OHD associated with efavrienz is unclear and may differ on the basis of the baseline vitamin D status of the individual.

The data presented for ritonavir and tenofovir are less convincing. Exposure to these drugs was associated with a decreased odds of vitamin D insufficiency/deficiency in some but not all models. Furthermore, duration of exposure was not significantly associated with 25OHD levels. In vitro, protease inhibitors have been shown to inhibit 25-hydroxylase and 1-α hydroxylase in a dose-dependent and reversible manner [28], resulting in decreased production of $1,25(OH)_2D$. Ritonavir had the most pronounced effect on $1,25(OH)_2D$ levels in this in vitro model, although the ritonavir concentration used in the study (15 μM) is higher than serum concentrations of ritonavir that are detected when it is used to boost other protease inhibitors [29]. It would have been interesting for the authors to evaluate differences in 25OHD levels in participants receiving different protease inhibitor regimens, especially with and without ritonavir, similar to the comparisons in the in vitro study [28]. Tenofovir does not have a known effect on vitamin D metabolism. The authors hypothesize that tenofovir-induced proximal renal tubular dysfunction (PRTD) might reduce the 1-α hydroxylation capacity of the kidney, resulting in accumulation of 25OHD; however, they do not present evidence of an association between tenofovir use and renal insufficiency or $1,25(OH)_2D$ levels to support this assertion. The combination of protease inhibitors and tenofovir is more likely to result in dysregulation of mineral metabolism rather than alteration of 25OHD levels. Tenofovir-induced PRTD is associated with phosphaturia/hypophosphatemia, and $1,25(OH)_2D$ is an important counterregulatory hormone for hypophosphatemia; therefore, it is conceivable that inhibition of $1,25(OH)_2D$ production by protease inhibitors may exacerbate the dysregulation of mineral metabolism in patients receiving tenofovir. These discussions highlight the difficulty in sorting out the effects of specific ARTs or combinations of ARTs on vitamin D levels, especially with cross-sectional data.

In conclusion, this study by Dao et al contributes to the growing literature that suggests that use of certain ARTs, especially efavirenz, is associated with alterations in 25OHD levels. Several important questions remain unanswered, including the precise mechanism for the association between efavirenz and vitamin D, as well as interactions between different ARTs. Most importantly, the clinical relevance of altered vitamin D metabolism to skeletal and extraskeletal outcomes in this population remains unknown. Interventional studies of vitamin

D supplementation in HIV-infected individuals are crucial for better understanding of these relationships.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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