Study finds replacing efavirenz with darunavir improves vitamin D levels

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In the previous CATIE News bulletin, we reported that researchers in the U.S. found that exposure to efavirenz (Sustiva, Stocrin and in Atripla) might be linked to decreased vitamin D levels. Now, we report that researchers in several European countries have found that not only was exposure to efavirenz linked to low vitamin D levels, but that the amount of this vitamin in the blood improved after efavirenz was replaced by darunavir-ritonavir (Prezista-Norvir). Also, this second study has uncovered something novel—a link between exposure to AZT (zidovudine, Retrovir) and low vitamin D levels.

Study details

The Monet study recruited HIV-positive people who were taking anti-HIV therapy (commonly called ART or HAART) generally consisting of two nukes (nucleoside analogues) and either a non-nuke (NNRTI) or a protease inhibitor. All study volunteers had a viral load less than 50 copies/ml and no history of virologic failure. Once enrolled in Monet, participants were randomly assigned to receive one of the following regimens:

- monotherapy – darunavir-ritonavir 800-100 mg once daily
- ART – darunavir-ritonavir 800-100 mg once daily + two nukes

Monet recruited 256 volunteers; however, only 219 of them had vitamin D levels assessed before and after entry into the study and were therefore used for the vitamin D substudy. The average profile of participants in Monet was as follows:

- 20% females, 80% males
- 91% were White
- age – 43 years
- CD4+ count – 600 cells

The distribution of potent ART that volunteers took prior to entering Monet was as follows:

- efavirenz – 61 people
- lopinavir-ritonavir (Kaletra) – 52 people
- atazanavir (Reyataz)-ritonavir – 30 people
- saquinavir (Invirase)-ritonavir – 25 people
- nevirapine (Viramune) – 22 people

Additionally, 10 volunteers were taking a nuke combo of AZT + 3TC + abacavir co-formulated into one pill (Trizivir).

Commonly used nukes included AZT, tenofovir (Viread and in Truvada) and abacavir (Ziagen and in Kivexa).

Data analysis for the vitamin D substudy was done at the beginning and 96 weeks later. During this period no participants took vitamin D supplements.

Results
Low levels of vitamin D at the start of the study, just prior to using darunavir-ritonavir, were associated with the following:

- entering the study in January to April (when people in the northern hemisphere are less exposed to sunlight)
- being Black
- use of efavirenz
- use of AZT

These were all statistically significant factors.

Although participants who had used efavirenz had a 50% chance of severe vitamin D deficiency, this was not statistically significant.

**Results—Week 96**

After nearly two years of exposure to darunavir-ritonavir, there were fewer patients with severe vitamin D deficiency, regardless of what ART they had used previously.

Comparison of the two study regimens—darunavir-ritonavir monotherapy or with two nukes—revealed that they did not have different effects on vitamin D levels.

Among participants who previously had used efavirenz and/or AZT but who discontinued these drugs when they entered Monet, vitamin D levels rose by about 30% compared to participants who had used other nukes. This difference was statistically significant.

**Making sense of the findings**

In the present vitamin D substudy, participants were taking a wide variety of ART prior to entering Monet. This could have led to inadvertent biases when interpreting the data. However, the substudy was based on a randomized controlled trial and this greatly helps to reduce any bias that might have occurred when interpreting the results.

Other researchers have found in laboratory experiments with cells that efavirenz can suppress the activity of enzymes that are involved in processing vitamin D into its active form, vitamin D$_3$. Efavirenz appears to shift the pathway of vitamin D processing into the production of inactive compounds. This is a problem that also occurs with anti-seizure drugs.

In the past several years there have been case reports and cross-sectional studies that have linked the use of efavirenz to low vitamin D levels.

**Is efavirenz alone?**

The Monet study found a link between exposure to AZT and low vitamin D levels. This is the first report of such a problem from a randomized clinical trial and it needs to be confirmed in another study. Why AZT might have such an effect is surprising and not clear.

Other drugs commonly used by HIV-positive people also need to be assessed for their potential to affect the body’s production of vitamin D$_3$. So far, there has been a report of the antibiotic rifabutin (Mycobutin) apparently affecting vitamin D levels in one HIV-positive man. However, this will require confirmation.

**Not just in the north**

Several studies have documented vitamin D deficiency both in the pre-HAART era as well as in the past decade among HIV-positive people in the northern hemisphere. But even in tropical countries, such as Brazil, India and Tanzania, reports have emerged of vitamin D deficiency among HIV-positive people with or without exposure to ART.

**Clinical consequences**

The clinical effects of vitamin D deficiency in the short-term are unclear. For the vast majority of efavirenz users there have not been mass reports of bone fractures. Efavirenz is a drug with excellent anti-HIV activity and is a
very convenient and effective part of many regimens, so, based on reports so far, it does not make sense for doctors caring for their patients to immediately switch to other anti-HIV therapies.

However, it may be prudent for all HIV-positive people to have vitamin D levels assessed and, if necessary, supplements of vitamin D₃ can be prescribed to bring levels within the normal range. To raise vitamin D₃ levels in HIV-positive people with deficiency, doses of at least 2,000 IU/day may be necessary, according to doctors in the Netherlands and U.K. Even with such doses it may take months for vitamin D levels to return to normal in some people. Occasionally, much higher doses for shorter periods may be needed.

**Future directions**

The vitamin D substudy of Monet does not prove that exposure to efavirenz or AZT causes vitamin D deficiency. However, it does strengthen the signal linking efavirenz to vitamin-D-related problems. Clinical trials need to be specifically designed to explore the impact of efavirenz on vitamin D both in the blood and at the cellular level, particularly in organs that are involved in vitamin D production and processing such as the skin, liver and kidneys. Also needed are clinical trials that assess the safety and effectiveness of different doses of vitamin D₃ over the long-term. This is necessary, as one short-term study unexpectedly found an increase in insulin resistance (pre-diabetes) in HIV-positive people given 2,000 IU/day of vitamin D₃. In contrast, in a placebo-controlled trial in HIV-negative women, 4,000 IU/day of vitamin D₃ supplementation did not increase insulin resistance and appeared to have reduced their risk for developing diabetes.

**From HIV negative to HIV positive**

Experiments with animals and observational studies among HIV-negative people suggest the possibility that low levels of vitamin D₃ may play a role in a variety of conditions, such as some cancers as well as inflammatory and cardiovascular diseases. Unfortunately, observational studies, no matter how large, are limited by their design to finding associations. They cannot prove cause and effect; in other words, they cannot prove that vitamin D does or does not reduce the risk of certain health conditions. Because inflammation seems to be a feature of HIV infection, it may be prudent to begin to develop and conduct robustly designed studies assessing the long-term impact of vitamin D₃ on inflammation, cardiovascular disease, insulin resistance, cancers and survival in HIV-positive people.

—Sean R. Hosein

**REFERENCES:**


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