Truvada as PrEP Tied to Only Modest Bone Density Decline

A new analysis also found a correlation between higher adherence to the daily drug regimen and greater bone density loss.

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A new, close look at the effect on bone mineral density (BMD) of Truvada (tenofovir disoproxil fumarate/emtricitabine) as pre-exposure prophylaxis (PrEP) found that higher adherence to the daily drug regimen is tied to a greater decline in BMD. That said, even those HIV-negative people who took Truvada daily in a major study experienced only modest declines in BMD.

No study of PrEP to date has found that Truvada is associated with an increased risk of fracture among HIV-negative individuals. Such an outcome would be what is known as a clinically significant result.

Publishing their findings in AIDS Research and Human Retroviruses, Matthew Spinelli, MD, of the University of California , San Francisco, and colleagues analyzed data from a metabolic and bone substudy of the iPrEX open-label extension (OLE) study of transgender women and cisgender men who have sex with men (MSM). The participants in the placebo-controlled iPrEx study, which was published in 2010 and first proved PrEP's efficacy, were invited to continue taking Truvada for prevention in this new phase. A median of 79 weeks passed between the end of iPrEx and participants' enrollment in the OLE phase. During that gap period, Truvada was not approved for PrEP in any country, so it is unlikely that many of the ultimate participants in OLE took the drug during that time.

The 290 substudy participants (out of the 1,225 people who elected to start PrEP in iPrEx OLE), were enrolled between June 2011 and June 2012 in seven of the 11 iPrEx OLE sites, including those in Cape Town; Chiang Mai, Thailand; Lima, Peru; Rio de Janeiro; San Francisco; and Chicago. They received dual X-ray absorptiometry (DXA) scans upon starting the open-label extension trial to determine their BMD at the hip and lumbar spine. They received repeat scans every 24 weeks until the end of their participation in the study. The final study visit was in December 2013.

There were adherence data—based on dried blood spot testing of the metabolized form of the tenofovir disoproxil fumarate component of Truvada—and at least one follow-up DXA scan for 254 substudy participants (87% of the total) over a median of 24 weeks.

The median age of the substudy participants was 31 years old. Nine percent were trans women, 40% were Latino, 18% were Asian, 15% were Black and 27% were white.

The researchers looked to a measure known as the Z-score, which compares an individual's BMD to the average BMD values based on age and sex as seen in the general population. A Z-score below -2.0 indicates a BMD lower than is expected based on an individual's age and sex. The median Z-score upon entry into the substudy was -0.7 at the spine and 0.2 at the hip. At that time, 9% of the participants had Z-scores lower than -2.0 at either the spine or the hip.

During the substudy, 3% who did not previously have one developed a Z-score below -2.0. All of those who newly developed a low Z-score had quantifiable levels of metabolized tenofovir, with 57% of them likely taking at least four doses of Truvada per week based on their drug levels.

Participants did not experience BMD declines after their 24-week DXA assessment.

None of the participants experienced a bone fracture.

Stratifying the participants based on their estimated level of adherence to Truvada, the researchers found that there was a dose-dependent association (meaning taking more doses per week was linked to a stronger effect) with declining spine BMD. There was also a dose-dependent decline in hip BMD by the 24-week mark. But by the end of the study, there was no statistically significant association between adherence to PrEP and the decline in BMD at the hip.

There was no difference in the percentage of BMD between those who started the study with low versus normal Z-scores.

After adjusting the data to account for various factors that might have affected bone mineral density, the study authors found that by the end of the study, the increasing level of adherence to the daily Truvada regimen was the only factor they could identify that was associated with a decline in spine BMD. This association did not differ between the MSM and trans participants. As for the decline in hip BMD, taking an estimated four to six doses of Truvada weekly, compared with having no detectable drug, was associated with a statistically significant decline.

The average decline in spine BMD was -1.15% among those likely taking Truvada daily, 0.53% among those estimated to be taking four to six doses weekly, -0.46% among those estimated to be taking two to three doses weekly and 0.26% among those estimated to be taking less than two doses weekly. Those likely not taking PrEP saw an average 0.72% increase in spine BMD. At the hip, the respective declines in BMD at each of the adherence levels was -0.50%, -0.75%, -0.7%, -0.43% and -0.03% among those estimated to be taking PrEP daily, four to six times weekly, two to three times weekly, less than two times weekly and none at all.

The study authors found that the level of BMD decline seen among those taking Truvada daily "was reassuringly similar or lower than that observed in most prior PrEP studies."

"For those planning prolonged daily PrEP use who are at high risk of fracture," the study authors

wrote, “alternate PrEP strategies such as tenofovir alafenamide–based PrEP could be considered once available.”

On that note, Descovy’s (tenofovir alafenamide/emtricitabine) use as PrEP will likely be approved late this year.

Research indicates that Descovy, compared with Truvada, is associated with improved biomarkers of bone and kidney health, thanks to the updated version of tenofovir contained in the former drug. But since neither drug has ever been associated with fracture among HIV-negative people, it is unclear whether using Descovy over Truvada as PrEP will prevent such a rare outcome.

Referring to the on-demand PrEP dosing strategy, also known as PrEP 2-1-1, the study authors continued: “Dose-limiting strategies such as intermittent [Truvada]-based PrEP could also potentially reduce risks of bone toxicity if that strategy were preferred by the PrEP users. However, given the modest declines seen with even very high adherence in our study, these differences are likely clinically significant only for those at [the] higher risk of bone toxicity.”

The investigators said those at high risk of fracture based on other risk factors and health conditions, such as stimulant or glucocorticoid use, should be closely monitored while taking Truvada as PrEP.

“Alternative PrEP agents, once available,” the investigators stated, “could also be considered in those at risk of bone or [kidney] toxicity.”

To read the study abstract, click here.

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http://beta.docker.poz.com/article/truvada-prep-tied-modest-bone-density-decline