

Changes in bone density among HIV-negative men, some of whom used tenofovir

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A placebo-controlled clinical trial called iPrEX was conducted to assess the safety and effectiveness of daily Truvada (a fixed-dose combination of two drugs in one pill: tenofovir + FTC) in reducing the risk of HIV transmission among gay and bisexual men and transgender women. Overall, Truvada, as part of a comprehensive prevention package (which included regular testing and treatment of sexually transmitted infections, HIV prevention counseling and so on), reduced the risk of becoming HIV positive by about 44%. For further details about iPrEX, see the following CATIE resources:

- Truvada for HIV prevention – some good news but caution is still needed
- Pre-exposure prophylaxis (PrEP) Fact Sheet

Tenofovir is one of the drugs in Truvada, and over the past decade there have been reports of less-than-normal bone mineral density (BMD) in some HIV-positive tenofovir users. So researchers involved with the iPrEX study in San Francisco, California, conducted analyses of bone mineral density among a subset of iPrEX participants before and after their exposure to tenofovir. All participants in the subset were men who have sex with men (MSM). The study team noted that about 10% of participants had thinner-than-normal bones. Low bone mineral density was associated with substance use *before* participants began to take Truvada. Once in the study, about 13% of tenofovir users and 6% of placebo users had their bone mineral density decrease by more than 5%.

Study details

Bone density is primarily assessed using low-dose X-ray scans called DEXA (dual energy X-ray absorptiometry). DEXAs were done at the start of the study and 12 and 24 months later.

Also, study staff interviewed participants so that other health-related information could be gathered. In total, data from 210 MSM were used.

Understanding DEXA results

Based on the results of DEXA scans, bone density results are given T or Z scores. T scores compare a person's bone mineral density to those in a young population of similar gender and race/ethnicity. Z scores compare a person's bone mineral density to those of other people of similar age, weight, race and gender.

Scores (or BMD) with a minus sign in front of them have less-than-ideal bone density. For instance, a score between -1 and -2.5 indicates osteopenia, and a score below -2.5 indicates osteoporosis.

Results – Baseline

Researchers were surprised to find that about 10% of participants (20 men) had serious loss of bone mineral density, mostly in the spine but also some in the hip and thigh, even before they had been

exposed to Truvada.

The study team had expected to find that about 5 out of 210 men (2%) had a serious degree of bone loss.

They conducted additional analyses in blood samples of 16 of these 20 men with unexpectedly low bone mineral density and found that two men had extremely low vitamin D levels and another two men had very low levels of testosterone. Both of these are factors in osteopenia and osteoporosis. However, these analyses don't explain the findings in the majority of men, so the research team conducted statistical analyses of behaviour and reduced bone mineral density. They found that men with the following behaviours were highly likely to have thinner-than-normal bones:

- use of amphetamines (speed, crystal meth)
- inhaling poppers (amyl nitrate) or glue

In contrast, men who reported that they took supplemental vitamin D and calcium were significantly less likely to have low bone mineral density.

Results – Tenofovir

Overall, participants who used tenofovir developed a statistically significant decrease in bone mineral density, averaging about 1%, at the hip or spine.

However, among some participants a greater degree of bone loss occurred, as follows:

- 36% of men taking tenofovir and 20% taking placebo lost more than 3% of BMD where the thigh bones meet the pelvic bones
- 14% of men taking tenofovir and 3% taking placebo lost more than 3% of BMD in their hips

These differences were statistically significant; that is, not likely due to chance alone.

Results – Fractures

As reduced bone density is associated with an increased risk for fractures, researchers investigated cases of broken bones, distributed as follows:

- Truvada users – six people had eight fractures
- placebo users – four people had four fractures

In all cases, fractures were due to trauma (accidents or violence) and not to tenofovir.

The iPrEX bone study

In this analysis of bone health, about 10% of HIV-negative MSM in the study had reduced bone mineral density *before* they were exposed to Truvada. This is about five times greater than would be expected. This finding calls for further study of HIV-negative MSM to better understand factors associated with reduced bone mineral density.

Overall, tenofovir's effect on bone mineral density was small and not linked to a statistically increased risk for fractures. However, it is noteworthy that in a substantial subset of men who received tenofovir, decreases of more than 3% in bone mineral density were detected over the course of the study.

The findings from iPrEX suggest that reduced bone mineral density may be an unrecognized problem among other men who are at high risk for HIV. A recent Dutch study may have suggested something similar.

The Dutch bone study

In that study, researchers in Amsterdam assessed a group of 33 MSM in whom HIV was detected very early, as part of a study. All the men were HIV negative six months prior to their most recent HIV test. DEXA scans done between 21 and 45 days after these men became HIV positive found high rates of osteopenia (45%) and osteoporosis (6%). Blood tests did not find elevated levels of proteins (or markers) associated with inflammation, so it is unlikely that HIV-related inflammation was responsible for such a large decrease in bone density occurring in such a short time after HIV infection. Certainly the high viral loads seen in early HIV infection may have played a role in bone thinning. However, it is also possible that some of these men had decreased bone mineral density prior to HIV infection. Some of them had less-than-ideal body weight, a factor associated with reduced bone density.

Further studies are needed in men at high risk for HIV infection to understand why the incidence of low bone mineral density is greater than expected. Similar studies need to be done for women.

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