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# Zolodrenic acid can prevent early bone loss in HIV patients on antiretroviral therapy

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A single dose of the drug zoledronic acid was found to inhibit the bone loss that is common in HIV-infected patients and that is increased during the first two years of treatment with antiretroviral therapy (ART). Bone loss also leads to a higher rate of fracture in HIV-infected individuals.

Results of the Phase II clinical trial were presented Feb. 23 at the 2016 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston. Study co=authors were Igho Ofotokun, PhD, associate professor of medicine (infectious diseases) at Emory University School of Medicine and M. Neal Weitzmann, PhD, associate professor of medicine (endocrinology) at Emory School of Medicine and the Atlanta Veterans Affairs Medical Center.

Researchers studied HIV positive individuals, ages 30 to 50 years, who did not have osteoporosis, had no history of immunological disease other than HIV, had serum vitamin D and calcium levels within the normal range, and normal CBC and blood chemistry profiles. The study excluded patients who had osteoporosis, those with planned or recent invasive dental procedures, active peptic ulcer disease or recent history of GI bleed, and pregnant or breastfeeding women.

Outcome measures included a marker of bone loss (CTx), and osteocalcin, a marker of bone formation. A bone marrow density scan was used to measure osteopenia and osteoporosis. The study also measured tolerability and safety.

The researchers assessed 343 individuals for eligibility, and 63 were selected and randomized to receive either ART and placebo, or ART and zoledronic acid.

Treatment with zoledronic acid was associated with a 73 percent and a 65 percent reduction in bone loss relative to placebo at 12 weeks and 24 weeks respectively, an effect that lasted throughout the 48 weeks of the study.

Enhanced bone loss was seen in almost all participants in the placebo arm of the study, while no participant in the treatment arm had an appreciable rise in bone loss. Participants in the placebo arm had a compensatory increase in bone formation, which was an expected result, but bone formation was flat in the treatment arm.

Treatment with zoledronic acid was associated with an eight percent increase in lumbar spine bone marrow density at 12 weeks relative to the placebo arm, with an 11 percent increase at 24 and 48 weeks.

Bone loss was higher in men compared to women in the placebo arm, and the protection against bone loss was higher in men than in women in the treatment arm.

Treatment did not impact the rate of viral suppression or immunologic response.

"We are encouraged that our protocol was able to prevent bone loss in HIV patients on ART therapy," says Ofotokun. "These effects occurred early and last through 48 weeks, which is the period when ART-induced bone loss is most intense. This could be an opportunity for effective prophylaxis for preventing bone loss."

Ofotokun notes this was a small sample size conducted at a single site,

with a mostly male, African-American population, and a short duration of 48 weeks. The researchers hope to conduct a larger multicenter study to confirm their findings.

The clinical trial in humans was based on positive results of a study in mice published in *Nature Communications* in Sept. 2015. In that paper, Weitzmann, Ofotokun, and their colleagues described bone loss similar to that observed in humans following the reconstitution of the T cell population in immune-compromised mice (similar to T-cell expansion following ART). Their findings suggested that the bone loss associated with ART might be caused by inflammatory responses resulting from recovery of the immune system, rather than by the antiretroviral drugs themselves.

In the mouse study, a single injection of zoledronic acid was able to prevent bone loss without impairing the rebuilding of the immune system.

The current study was sponsored by the National Institute on Aging of the National Institutes of Health. Novartis provided the study drug and placebo, but did play any additional role in the study.

**More information:** Ighovwerha Ofotokun et al. Role of T-cell reconstitution in HIV-1 antiretroviral therapy-induced bone loss, *Nature Communications* (2015). DOI: 10.1038/ncomms9282

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