**Kaletra + raltegravir—does sparing some nukes help bones?**

Once potent combination therapy for HIV (commonly called ART or HAART) is initiated, several clinical trials have found that bone mineral density tends to decrease, usually between 2% and 6%, and then stabilize. The reasons for this initial decrease are not clear.

Some studies suggest that exposure to the anti-HIV drug tenofovir (Viread and in Truvada, Atripla, Complera and Stribild) may be linked to decreased bone mineral density (BMD) in some people. However, it is important to bear in mind that most HIV-positive people who use tenofovir in prospective clinical trials have not developed decreased BMD and subsequent fractures.

**The Progress study—a summary**

Researchers in several countries conducted a pilot study called Progress to compare the effect of the following two regimens:

- lopinavir-ritonavir (Kaletra) + Truvada (a fixed-dose combination of tenofovir + FTC)
- lopinavir-ritonavir + raltegravir (sold as Isentress)

When it was first introduced in 1996, the drug ritonavir (sold as Norvir) was meant to be used at very high doses as part of ART. However, at such high doses ritonavir has many side effects. Today when ritonavir (Norvir) is used, it is generally taken in relatively small doses to help boost the level of another drug, usually an HIV protease inhibitor. When used in this way ritonavir does not have anti-HIV activity, as it is merely a boosting agent. The other drug that is boosted has powerful anti-HIV activity.

In all cases in this study, Kaletra was taken twice daily, as was raltegravir. Truvada was taken once daily.

Researchers recruited 209 volunteers who had not been previously exposed to treatment and monitored them for up to two years.

On average, participants were about 40 years old and mostly male (85% men, 15% women).

Similar proportions of participants (71%) taking each regimen achieved a viral load less than 40 copies/ml at week 96, according to an assessment called the Food and Drug Administration’s “snapshot” analysis.

Participants who experienced virologic failure were distributed as follows:

- Kaletra + Truvada – five cases; drug-resistant HIV was detected in one person
- Kaletra + raltegravir – eight cases; drug-resistant HIV was detected in three people

Participants had their CD4+ counts increase by 300 cells/ml by the end of the study.

**Side effects**

In general, side effects reported by patients were similar with each regimen. According to researchers, the most common side effect of “at least moderate severity was diarrhea,” distributed as follows:

- Kaletra + Truvada – 16% of participants
- Kaletra + raltegravir – 8% of participants

They also stated that the following proportions of participants left the study prematurely due to side effects:

- Kaletra + Truvada – 4% of participants
Kaletra + raltegravir – 5% of participants

Overall, two participants taking each regimen (for a total of four participants) left prematurely because of diarrhea. Thus, about 2% of participants taking each regimen left prematurely because of diarrhea.

The proportions of participants taking each regimen who took anti-diarrhea medicines were distributed as follows:

- Kaletra + Truvada – 29%
- Kaletra + raltegravir – 27%

Elevated levels of lipids (cholesterol and triglycerides) in the blood are common when protease inhibitors are used. Rates of severely elevated levels of total cholesterol were distributed as follows:

- Kaletra + Truvada – 14%
- Kaletra + raltegravir – 17%

Rates of severely elevated triglycerides were distributed as follows:

- Kaletra + Truvada – 5%
- Kaletra + raltegravir – 10%

**Focus on overall changes in bone density and fractures**

Among participants for whom bone mineral density scans were available, researchers noted that bone thickness was generally similar at the start of the study. However, at the 96-week mark, on average, BMD had changed as follows:

- Kaletra + Truvada – minus 2.5%
- Kaletra + raltegravir – + 0.7%

This difference was statistically significant; that is, not likely due to chance alone.

There were four fractures during the study that were distributed as follows:

- Kaletra + Truvada – one fracture each in the foot, arm and wrist
- Kaletra + raltegravir – one fracture in the hand

The study was not designed to assess the statistical importance of fractures so we cannot draw firm conclusions about their distribution and if that has any link to the regimens used in this pilot study. It is possible that the distribution of fractures may simply have been due to chance.

Researchers also assessed what they termed “clinically significant loss of bone mineral density.” These were cases where participants lost BMD of 5% or more by the 96th week of the study. Overall, 12% (19 of 160 participants) had a large decrease in BMD during the study, distributed as follows:

- Kaletra + Tenofovir – 16 of 82 (20%) participants who had BMD X-ray scans taken at the start and end of the study
- Kaletra + raltegravir – 3 of 78 (4%) participants who had BMD X-ray scans taken at the start and end of the study

Factors that were statistically linked to having decreased BMD included the following:

- being 40 years or older
- being white
- having a CD4+ count less than 200 cells/ml when starting ART

**Bone proteins**

Although bone may feel stiff and hard, it is not dead. Bone tissue is dynamic—in adults small portions of bone are always being torn down and replaced. Researchers refer to this tearing down and building up of bone as “bone turnover.” There are proteins in the blood and urine that are associated with bone turnover and can be assessed in
research studies. In Progress, researchers assessed the following markers of bone turnover at several points throughout the study:

- CTx (C-terminal telopeptide of type 1 collagen)
- OC (Osteocalcin)
- P1NP (procollagen type I N-propeptide)
- BSAP (bone-specific alkaline phosphatase)

Bone turnover markers were, on average, elevated in all participants, reaching their highest level at week 48 of the study.

Early changes in some bone turnover markers were connected to a significant loss of BMD (at least 5%) at week 96, specifically these changes at week 4:

- elevated levels of CTx

Changes at week 4 in the following markers appeared to be protective from significant loss of bone density:

- elevated levels of OC and P1NP

These findings in bone markers seem novel and deserve further study in clinical trials with other medicines.

The Progress study and its sub-analyses provide important signals about changes that bones undergo once ART is initiated. Such changes should be studied with other commonly used regimens. Findings from Progress suggest that replacing Truvada with raltegravir may lead to very modest increases in BMD rather than significant loss of bone.

Bear in mind the following points:

1. The backbone of this study was the drug Kaletra. For much of the past decade in high-income countries, Kaletra was widely used both for the initiation of HIV treatment and in treatment-experienced patients. However, other treatment options became available in the past decade and Kaletra no longer holds the dominant position that it once did. Thus, while the Progress study has produced very interesting findings, it is unlikely that doctors will change the regimens of large numbers of patients to a combination of Kaletra (and raltegravir) based on the data from Progress.

2. Raltegravir costs more than Truvada. It is unlikely that formularies that subsidize the cost of HIV treatment would be willing or able to financially sustain a switch from Truvada to raltegravir among the majority of their patients over the long term.

3. The Progress study’s results about bone mineral density in raltegravir users find some support from a study in Australia. There, researchers conducted a pilot study with 37 patients who had low BMD and who switched the tenofovir in their regimens for raltegravir. Participants were monitored for 48 weeks. After the switch, researchers found that BMD increased by 2.5% to 3% in the hip and spine, respectively. Levels of bone turnover markers decreased at weeks 24 and 48 after the switch. However, the Australian study was small and of short duration and it was not randomized. As a result of these shortcomings, its findings can be at best considered suggestive not definitive. Still, it appears that for some HIV-positive patients, raltegravir is associated with modest increases in BMD when it has replaced tenofovir.

Overall, the findings from Progress and the Australian study are intriguing but require further larger randomized studies for confirmation.

Gilead Sciences, the manufacturer of tenofovir, is testing a new form of tenofovir called TAF. Interim results from clinical trials have led Gilead Sciences to suggest that TAF may be safer for the bones and kidneys than tenofovir.

REFERENCES:


—Sean R. Hosein


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