Heart Rhythm Disturbances the Same for All Protease Inhibitors

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All Norvir (ritonavir)–boosted protease inhibitors (PIs), not just Kaletra or Norvir-boosted Reyataz, can cause heart rhythm disturbances, according to a new analysis by Strategies for Management of Antiretroviral Therapy (SMART) study researchers, published online by the journal *AIDS*. The data, which contradict the results of other studies that didn't find other PIs to be associated with heart rhythm abnormalities, also suggest that heart rhythm normalizes after discontinuing the meds.

Heart rhythm disturbances can be harmful. In the least less serious cases, they can lead to dizziness, fainting or may not cause any symptoms at all. In the worst cases, they might require a pacemaker or even result in sudden death.

A person's heart rhythm is measured using a simple machine called an electrocardiograph (ECG). It evaluates the electrical activity of the heart using electrodes applied to the skin. Two measures of concern are the QTc interval and the PR interval. When the QTc interval is shorted, or the PR interval prolonged, an abnormal heart rhythm is diagnosed.

In the past two years, the U.S. Food and Drug Administration (FDA) has warned that two protease inhibitors—Kaletra (lopinavir/ritonavir) and Norvir-boosted Reyataz (atazanavir)—can cause such heart rhythm disturbances. As to whether other protease inhibitors cause similar problems, studies have yielded mixed results. What's more, it hasn't been clear whether discontinuing protease inhibitor-based regimens reverses the problem.

To provide a deeper and better understanding of the problem, Elsayed Soliman, MD, from the Wake Forest School of Medicine in Winston Salem, North Carolina, and his colleagues analyzed data involving 3,719 HIV-positive people who participated in the SMART study. In SMART, participants either went on and stayed on ARV therapy—using either a PI-based regimen or a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen—or delayed therapy until their CD4s fell to 200 and then stopped therapy again if the CD4s went back above 350. This allowed Soliman's team to look not only at the effects of both drug classes, but also at the effects of starting or stopping various HIV medications.

The average age of SMART participants in the analysis was 44. Just under half were on an NNRTI-based regimen, and 31 percent were taking a Norvir-boosted PI. In those taking a PI, the majority

were taking either Kaletra, Norvir-boosted Reyataz or Norvir-boosted Invirase (saquinavir). People on other PI regimens were classified as “other protease.”

When a variety of factors were taken into account, including race, age and blood pressure, there were no differences in QTc or PR intervals between the various PI regimens at either 12 or 24 months after starting treatment. In all cases, however, the QTc was shorter and the PR was longer in those on a PI than in people taking an NNRTI. This confirmed the findings of previous studies that the problem is unique to the PI class of drugs, but it also demonstrated that no single PI is apparently better than any other in this regard.

As for the effects of stopping PI-based therapy, Soliman’s group found that one particular measurement of QTc improved while those measured using another method did not. The results were clearer in regards to the PR interval, which shortened after people stopped taking a PI-based regimen.

The authors state that the clinical significance of their findings is unknown. There were no cases of sudden death that could be attributed to PI use and changes in QTc interval. Moreover, in the average HIV-negative population, even a 20 millisecond (ms) increase in the PR interval is associated with only an 8 percent increase in all-cause mortality. The average increase seen in this study was only 3ms.

For this reason, the authors are recommending further studies to illuminate the biological mechanism by which PIs affect heart rhythm and to tease out any possible effect on clinical health. They conclude: “These results should not limit the use of protease inhibitor/ritonavir regimens when indicated.”

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