ViiV Integrase Inhibitor Dolutegravir Is Better Twice-Daily for Treatment-Experienced People

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ViiV Healthcare's experimental integrase inhibitor, now called dolutegravir (S/GSK-572), works better when taken 50 milligrams (mg) twice-daily than when taken as 50 mg once-daily in people who have heavy resistance to other integrase inhibitors, notably Merck's Isentress (raltegravir) and Gilead's still-experimental elvitegravir. These data were presented Wednesday, March 2, at the 18th Conference on Retroviruses and Opportunistic Infections (CROI) in Boston.

In a presentation last summer, at the XVIII International AIDS Conference in Vienna, researchers offered a first glimpse for how well dolutegravir worked in both people new to treatment and in people whose virus was resistant not only to other classes of drugs, but also to both Isentress and elvitegravir. While dolutegravir worked extremely well in people who'd never taken antiretrovirals (ARVs) before, and in those with limited integrase inhibitor resistance, its performance remained questionable in people with extensive integrase inhibitor resistance.

That study in treatment-experienced people, called VIKING Cohort I, had people with at least some level of integrase resistance add 50 mg of dolutegravir once a day to a failing regimen for 11 days, and then after 11 days substitute a new optimized background regimen for the failing background drugs. The study was designed to continue for another 48 weeks after people optimized their regimens. The goal of the initial analysis was to determine the proportion of people who had either a viral load under 400 copies or at least a 0.7 log drop in virus by day 11.

In the preliminary analysis, ViiV researchers found that people who had extensive integrase resistance, particularly the Q148H/K/R mutation in addition to at least two other integrase mutations, were far less likely to reach either goal by day 11. While all of the 18 people with lighter resistance had at least a 0.7 log drop or an undetectable viral load by day 11, only 3 of 9 of those with extensive integrase resistance did so. This led researchers to test whether upping the dose, to 50 mg twice-daily, might do better against heavy resistance.

In the study, VIKING Cohort II, presented at this year's CROI, researchers used the exact same study design as in cohort I, except for the change in dosing. The study also required that people in the study had to have at least one fully active drug that they could add to their regimens when the background drugs were switched after day 11.

Presenting on behalf of the study team, Joseph Eron, MD, from the University of North Carolina in Chapel Hill, reported that the increased dose made a significant difference. In VIKING Cohort II, roughly half the participants had mild integrase resistance and the other half had heavy resistance, with the Q148 mutation plus at least one other integrase mutation or another mixture of multiple mutations.

Taken as a whole, Eron reported, 96 percent of the people in the twice-daily dosing cohort reached the viral load reduction goals compared with only 78 percent in the older once-daily dosing cohort. What's more, all the people with heavy integrase resistance responded to dolutegravir in the twice-daily cohort, whereas only one third responded in the once-daily cohort.

Eron cautioned that the once-daily and twice-daily groups differed in an important respect. When Eron and his colleagues tested each person's virus in a test tube against dolutegravir, there was a wider range of responses in the once-daily cohort versus the twice-daily cohort. This meant that there were at least a few people in the once-daily cohort whose virus was much less susceptible to the drug than in the twice-daily cohort. While this may not be relevant, it is possible that at least some of the improvement in treatment response in the twice-daily cohort could be due to this difference.

Dolutegravir was very well tolerated in the study, and there were no differences in side effects between those in the once- and twice-daily groups.

Eron concluded by stating that dolutegravir showed greater activity against the virus when dosed twice-daily, but that a longer-term (24 week) analysis will give a more complete picture. ViiV has selected the twice-daily dose for a large Phase III trial that is now underway, he added.

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