HIV Integrase Inhibitor Dolutegravir Showing Well in First-Time Treatment Takers

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ViiV Healthcare's experimental integrase inhibitor dolutegravir (S/GSK-572), using the highest dose studied in the SPRING-1 clinical trial, was at least as effective as efavirenz (found in Sustiva and Atripla) in controlling HIV levels with fewer side effects over 48 weeks. These data from the study involving first-time HIV treatment takers were presented Tuesday, July 19, at the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention in Rome.

Although the current crop of recommended antiretroviral (ARV) drugs is quite potent, each drug has its disadvantages. Some have troublesome side effects, while others must be taken several times a day. Needless to say, there's a demand for new treatments that can be easily joined with other drugs into a single pill that can be taken once daily and that has minimal side effects.

One candidate with the potential to meet all of those challenges in dolutegravir. It is a second-generation integrase inhibitor that can be taken once daily, without the need for blood-level boosting by Norvir (ritonavir), and that so far appears to have minimal side effects. What's more, the daily dose is small enough that it should be easy to combine with other drugs into a single pill—a prospect that is currently being explored, in the forum of 572-Trii.

To determine dolutegravir's efficacy in people who hadn't taken ARV therapy before, Jan van Lunzen, MD, from the University Medical Center in Hamburg-Eppendorf, Germany, and his colleagues randomized 205 people to take either an efavirenz plus either Truvada (tenofovir plus emtricitabine) or Epzicom (abacavir plus lamivudine), or Truvada/Epzicom plus one of three potential doses of dolutegravir: 10 milligrams (mg), 25 mg or 50 mg. The participants in the study were mostly white males, their average age was about 37, and their average CD4 count was 324.

During the first three months of the study, all doses of dolutegravir reduced viral loads to levels below 50 copies—undetectable—more effectively than Sustiva, which isn't uncommon among integrase inhibitors. Whereas more than 90 percent of those receiving dolutegravir had undetectable viral loads by the 146h week of treatment, less than 60 percent of those in the Sustiva group had achieved this early milestone.

After 48 weeks of treatment, undetectable viral load rates in the four groups were comparable.

The percentage of people with viral loads less than 50 copies at 48 weeks was 91 percent with the 10 mg dose, 88 percent with the 25 mg dose and 90 percent with the 50 mg dose. Among those receiving Sustiva, 82 percent had viral loads below 50 copies after 48 weeks.

Significant increases in CD4 counts were reported in all study groups through 48 weeks of treatment.

There were three study-defined virologic failures among the 150 patients receiving dolutegravir. Two occurred in the 10 mg group, and one occurred in the 25 mg group. No HIV mutations known to confer resistance to integrase inhibitors was documented in any of the patients; only in one patient was there a reported mutation associated with resistance to emtricitabine and lamivudine.

No patients in the 50 mg dolutegravir group had a confirmed viral load above 400 copies through week 48 of the study.

About 20 percent of volunteers receiving Sustiva, compared with 8 percent of those receiving dolutegravir, experienced moderate-to-severe side effects in the study. Gastrointestinal problems, central nervous system irregularities and skin rash appeared to be more common among those taking Sustiva.

Side effects leading to withdrawal from the study or a change in ARV therapy occurred in 8 percent of those in the Sustiva group, compared with 1 percent of those in the combined dolutegravir groups.

Severe lab abnormalities were rare, occurring in 12 percent of those receiving dolutegravir and 14 percent of those taking Sustiva. However, small changes in serum creatinine—a component of muscle and indicator of kidney function—were reported among those taking dolutegravir. This is likely because dolutegravir inhibits a component of the kidneys response for excreting creatinine, which is similar to at least two approved drugs: the antibiotic trimethoprim and the acid reflux medication cimetidine.

Patients treated with Sustiva were significantly more likely to experience increases in total cholesterol and “good” HDL cholesterol; of note, “bad” choleserol levels rose by 0.55 mg/dL in the dolutegravir group, compared with an average 15.9 mg/dL increase in the Sustiva group. And while average triglyceride levels tended to drop by 10 points among those taking dolutegravir, they increased by more than 10 points among those taking Sustiva.

“In conclusion,” van Luzen reported, “dolutegravir administered once-daily without a booster showed a rapid and sustained response at all doses through week 48, with no integrase inhibitor mutations detected through 48 weeks.” He added that dolutegravir was well tolerated with fewer discontinuations than Sustiva, and with less pronounced effects of lipid levels.

The study will continue, as planned, for another 48 weeks. Studies involving treatment-experienced people living with HIV are also ongoing.

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